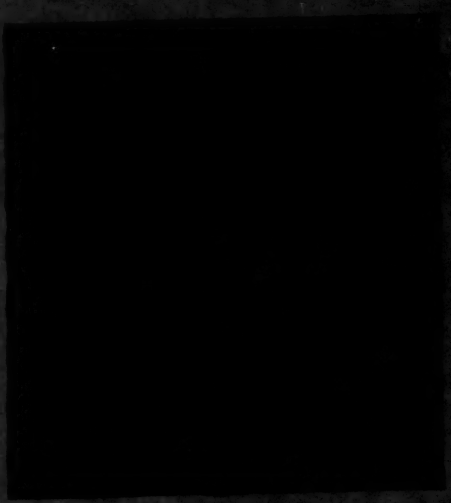

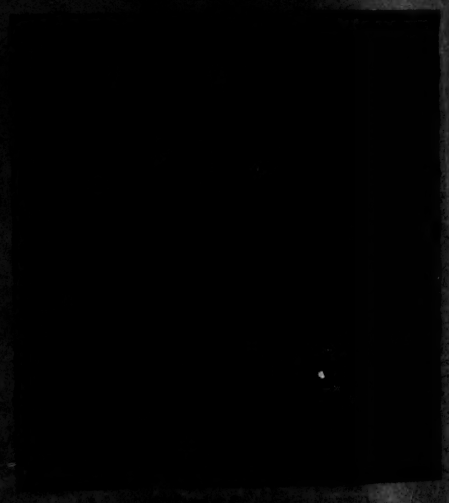

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OPHTHALMOLOGY

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COMMUNICATIONS

THE ROLE OF ASCORBIC ACID IN CORNEAL VASCULARIZATION*

BY

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Introduction

ALTHOUGH the cornea normally has no blood vessels, yet, under certain conditions, new vessels freely enter the substance of the cornea from the limbal plexus.

To explain this invasion many theories have been advanced. In riboflavin deficiency there is corneal vascularization. Since riboflavin is part of an oxidation enzyme system, Bessey and Wolbach (1939), and Johnson and Eckardt (1940), believe that anoxia is a stimulus for corneal vascularization. Campbell and Michaelson (1949) brought forward evidence that injury to the cornea close to the limbus sets free a humoral substance which then diffuses to the limbal vessels to stimulate new vessel formation. Julianelle and Lamb (1934) injected an antigen into the cornea of a sensitized animal. This evoked vascularization of the cornea.

* Received for publication January 16, 1950.

Mayer and Chaffee (1940) and Bacsich and Riddell (1945) look at the problem from a somewhat different angle. They believe that avascular tissues, cornea, cartilage, and Wharton's jelly, normally contain a substance inhibiting vascularization. One could postulate that injury to the cornea destroys or inhibits formation of this hypothetical substance, thus permitting invasion of blood vessels.

Cogan (1949), on the other hand, believes that vascularization is always preceded by oedema of the cornea involving the tissues of the limbus. The resulting reduction in the corneal tissue compactness allows invasion by blood vessels.

We recently studied the influence of lack of ascorbic acid on the rate of healing of heat injuries to the cornea of guinea-pigs (Campbell, Ferguson, and Garry, 1950). Our findings are summarized in Table I. We also found that there was marked persistence of structural weakness in the corneal stroma at the site of the lesion, presumably due to defective formation of collagen.

TABLE I

Time for Epithelial Healing of Deep Corneal Heat Injuries in Guinea-pigs

No. of wounds	Mean time of healing (hours)	Difference between controls and deficient animals (hours)
32 control 32 scorbutic	94·0 (± 6·02)* 125·8 (± 7·02)	31·8 (Highly significant)

't' = 3·43 $P < 0.01$ *Standard Error of the Mean.

During this investigation we took the opportunity to observe the incidence and progress of vascularization in the normal controls and in the scorbutic animals.

Method

Animals.—Female non-pregnant guinea-pigs were used. Their initial weights were between 450 and 650 g.

Diets.—The basal diet was crushed rat-cake cubes (Thomson, 1936) moistened with a little water. These cubes are free from ascorbic acid. To supplement this six drops of cod liver oil were added daily to the diet of each animal.

Ascorbic Acid.—To ensure that the cavies had a uniform initial level of saturation with ascorbic acid, 20 mg. ascorbic acid (Roche) were given orally in 2 ml. water once per day. This intake was given for 21 days in all cavies to obtain tissue equilibrium (Jones, Bartlett, Ryan, and Drummey, 1943).

Control Animals.—Control animals were injured after 21 days of saturation with Vitamin C and the daily intake of 20 mg. was continued thereafter.

Scorbutic Animals.—After a preliminary 21 days of saturation with 20 mg. ascorbic acid per day, the animals were given 0·5 mg. ascorbic acid every second day for a further 21 days. The injuries were then made to the animals, the dosage of 0·5 mg. ascorbic acid every second day being continued thereafter.

Apparatus.—The lesions were produced with a cautery made from a loop of 32 S.W.G. platinum wire. A predetermined constant voltage was fed to the cautery through a relay connected to the one second contacts of a Palmer A.C. time clock. This circuit allowed the current to flow through the cautery for exactly one second when required.

Technique.—The cornea was anaesthetized by instilling into the conjunctival sac two drops of a 2 per cent. pontocaine hydro-chloride solution. The operations did not appear to cause discomfort since the corneal reflex was never elicited and the animals remained quiet. No signs of distress appeared after the operation and in no case did infection occur.

The cold cautery was pressed firmly and vertically on the cornea 2 mm. from the limbus at 12 o'clock. The current was allowed to flow for exactly one second and the cautery was removed one second later. This gave a standard heat injury similar to that used by Campbell and Michaelson (1949). Histological examination showed that the resulting lesion was 1 mm. in diameter, and that the corneal epithelium and the anterior two-thirds of the substantia propria were destroyed.

All thermal injuries were carried out by the one operator, who was unaware whether a control or a scorbutic animal was being injured.

Examination of the injury, including degree of vascularization and of oedema, was made at eight hourly intervals by one observer with the aid of a binocular loupe and focal illumination. Once epithelial healing had occurred observations were continued at 24-hour intervals.

Results

During healing, vascularization of the cornea occurred in nine out of 32 eyes in control guinea-pigs, and in nineteen out of 32 eyes of deficient animals (Table II). The results were analysed by the

TABLE II

Incidence of Vascularization in the Control and Scorbutic Groups

Eyes	No. of vascularized corneae	No. of nonvascularized corneae
Control	9	23
Scorbutic	19	13

$\chi^2 = 5{\cdot}1$ $P < 0{\cdot}05$ (Significant).

χ-squared method ($\chi^2=5{\cdot}1$). Such a result could occur by chance only less than 1 in 40 times, and we may therefore presume that the greater incidence of vascularization in the scorbutic animals is significant.

This higher incidence might be due to the greater time required for healing in the group of deficient animals (Table I) for it is a common clinical observation in man that a corneal ulcer of long duration is more likely to induce corneal vascularization than one of short duration. If this explanation be true, then the eyes with vascularization will be associated with the injuries taking longer to heal. Table III shows the mean time of healing for the vascularized and nonvascularized eyes in the scorbutic group. The

TABLE III

Comparison of the Mean Time of WoundHealing in the Vascular and Non-vascular Corneæ in the Scorbutic Group

No. of Eyes	Mean time of healing (hours)	Difference in Means (hours)
19 vascular	127·6 (± 9·3)*	4·5
13 nonvascular ...	123·1 (±11·5)	(Not significant)

't' = 0·79 P > 0·4 *Standard Error of the Mean.

difference of 4·5 hours between the two groups is not significant. A gre difference in the means exists in the control group (Table IV). The difference of 17·7 hours is again, however, not significant. There is thus no conclusive evidence to suggest that, under

TABLE IV

Comparison of the Mean Time of Wound Healing in the Vascular and Non-vascular Corneae in the Control Group

No. of Eyes	Mean time of healing (hours)	Difference in Means (hours)
9 vascular	106·7 (± 13·8)*	17·7
23 nonvascular ...	89·0 (± 6·3)	(Not significant)

't' = 1·33 P > 0·1 *Standard Error of the Mean.

the conditions of this experiment, the greater incidence of vascularization in the scorbutic group is due to the longer time required for epithelial healing.

The onset of vascularization, the time of its maximum extent, and the time of disappearance all tended to be delayed in the scorbutic group compared with the control group (Table V).

TABLE V

Comparison of the Progress of Corneal Vascularization in Control and Scorbutic Groups

Vascularization	Mean Time (hours)		Difference in Means (hours)
	Control (9 eyes)	Scorbutic (19 eyes)	
Onset	33·7 (±8·30)*	52·6 (±8·79)*	18·9
Maximum ...	64·9 (±6·99)	79·6 (±9·31)	14·7
Disappearance	134·2 (±33.44)	146·5 (±21·56)	12·3

*Standard Error of the Mean.

The time of onset and the time of maximum oedema are shown in Table VI. The difference between the means of the times of onset is not significant. However, the scorbutic group did take

TABLE VI

Comparison of the Progress of Corneal Oedema in Control and Scorbutic Groups

Oedema	Mean Time (hours)		Difference in Means (hours)
	Control (32 eyes)	Scorbutic (32 eyes)	
Onset	17·3 (±2.53)*	16·5 (±1·83)*	0·8
Maximum ...	25·8 (±2·78)	42·8 (±6·22)	17·0

*Standard Error of the Mean.

significantly longer to reach the time of maximum oedema. The figures could be not be analysed for the time of disappearance of the oedema as some of the animals were killed for histological examination before the oedema had disappeared.

Discussion

The cornea is known to contain high concentrations of ascorbic acid, although there is some disagreement concerning the partition of ascorbic acid between the various layers of the cornea (Schmid and Bürki, 1943; Henkes, 1946; Pirie, 1946).

In experimental scurvy in guinea-pigs, ascorbic acid is known to disappear from the cornea in from 2 to 3 weeks (Henkes, 1946). Nevertheless, the cornea shows no obvious change even in severe and prolonged scurvy in human beings or in guinea-pigs. On the other hand, ascorbic acid is known to be necessary for formation of collagenous tissue in the repair of wounds in the cornea. Thus, the injuries we inflicted to the cornea possibly unmasked a deficiency not otherwise apparent. Presumably new formation of collagen makes additional metabolic demands which cannot be adequately met in a state of scurvy. Just as ariboflavinosis evokes spontaneous vascularization of the cornea, avitaminosis C may lead to vascularization when there is the extra metabolic demand following on injury.

Presumably failure to satisfy fully a metabolic need, however caused, leads to accumulation of metabolites. These metabolites may act as a direct stimulus to new blood-vessel formation. On the other hand, the metabolites may lead to oedema and opening up of the lamellae of the substantia propria, and thus permit invasion of blood vessels. Is it too much to suggest that the

accumulation of metabolites is the humoral factor postulated by Campbell and Michaelson (1949)?

This hypothesis is, of course, in the highest degree speculative, but our new finding that ascorbic acid deficiency significantly increases the incidence of vascularization of the cornea after injury does seem to warrant an attempt to find a common causal factor to explain the invasion of the avascular cornea by blood vessels in the conditions where such invasion is known to occur.

Summary

(1) A method is described for producing small standard heat injuries to the cornea.

(2) These injuries were inflicted on control and scorbutic guinea-pigs.

(3) New vessel invasion of the cornea following the injury occurred with significantly greater frequency in the scorbutic group than in the control group.

(4) The causal factor in new vessel formation in the cornea is discussed in the light of these findings. It may be that repair of an injury makes additional metabolic demands which cannot be met in a state of ascorbic acid deficiency. As a result, metabolites accumulate and evoke by some means, not yet fully understood, vascular invasion of the corneal substance.

We are indebted to Professor R. C. Garry for helpful criticism and encouragement. We also wish to express our indebtedness to Roche Products Limited for a liberal supply of ascorbic acid, and to the Rankin Medical Research Fund of the University of Glasgow for a grant to cover expenses.

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HEALING SERPIGINOUS ULCER OF THE CORNEA BY TOTAL CONJUNCTIVAL HOODING*

BY

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TREATMENT for serpiginous ulcer is a problem of ophthalmology which has not been adequately solved hitherto. As the literature reveals, it is a most interesting question for ophthalmologists. There is no bactericide, no theoretically promising operative method that has not been used to treat this disease. But most of these, however promising they seemed, generally proved no more efficacious than the methods known previously.

These failures are perhaps responsible for the fact that even a recent text-book, Thiel's "Lehrbuch der Augenheilkunde" (1948), in referring to operative methods for serpiginous ulcer, enumerates only obsolete and unsatisfactory methods such as cauterization, paracentesis, or Saemisch's keratotomy, without even mentioning the others. The conservatism of this text-book may also be due to the reason given by Brückner (1949) in his comments on Stein's lecture. Brückner says that grave cases of serpiginous ulcer are rarely seen in Switzerland. Since the prognosis is fairly good in most cases of incipient serpiginous ulcer, the writer of the chapter in question probably never saw that the operations he enumerates were not successful in grave cases. Almost every clinic has its own method of treating serpiginous ulcer, but these are generally of no avail in severe cases, as can be seen in the literature.

Earlier Methods of Treatment

The treatment for serpiginous ulcer may be conservative or operative.

Before penicillin was discovered and used, the conservative method consisted of local treatment: painting the ulcer with 20 per cent. $ZnSO_4$, sulphonamide drops or ointments, the administration of ethylmorphinhydrochloricum to increase the metabolism of the cornea, instillation of optochin hydrochloricum and other bactericide drugs into the conjunctival sac. Besides local treatment heteroprotein and sulphonamides may be given. Lately almost all the authors writing on the treatment of serpiginous ulcer have resorted to different systems of penicillin administration, a question I shall refer to later.

* Received for publication October 21, 1949.

The conservative therapy having been unsuccessful in many cases, new operative methods were devised.

Paracentesis soon proved to yield no satisfactory results.

Wessely (1926) tried to destroy the bacteria by steam cauterization. Before carrying out total hooding systematically, we used Wessely's method in many cases, but we were not satisfied with the results. In our experience this method may be effective with incipient ulcers, but not in severe cases. It even occurred that after steam cauterization the ulcer grew rapidly owing to exsiccation of the tissues.

Saemisch's keratotomy is generally resorted to as *ultimum refugium*. We saw panophthalmitis in more than one case as a consequence of this coarse method. When the progression of the ulcer came to a standstill after all, a thick adherent leucoma was present. We believe that in most cases this operation has no influence upon the growth of the ulcer.

Sondermann (1922) wanted to ensure the permanent escape of the aqueous by trephining the ulcer. By increasing the production of antibodies he hoped to promote healing of the ulcer. Before total hooding was introduced we saw in several cases that progression became definitely slower after the ulcer had perforated spontaneously. But in these cases too, the final result, after a long treatment, was severe leucoma or panophthalmitis. We believe that Sondermann's trephining across a section containing virulent bacteria is not without danger. We must also keep in mind that the lens may easily be injured by the trephining of the ulcer, the cornea having become thinner in an unequal way. Thus it seems improbable that this method would be often used in the therapy of serpiginous ulcer.

Similarly the results of hooding with a conjunctival flap as recommended by Kuhnt-Brückner are unsatisfactory. This method has been used with slight alterations by Löhlein (1931), Clausen (1931), Erggelet (1931), Rubbrecht (1931), Clerici (1934), and others, but it could not yield good results because of disadvantages to be discussed later in this paper.

Total Hooding

In 1941 I recommended a new and successful method for healing serpiginous ulcers: total hooding of the cornea with the conjunctiva. This operation devised for the healing of Mooren's ulcer, was published by Kreiker in 1933. At that time I had already reported 25 cases of severe serpiginous ulcer which had been successfully hooded in the course of one year. My publication had few repercussions in the literature, however, except for a report by Lawaetz (1943) of six cases of serpiginous ulcer successfully

treated by this method. In 1948, Kettesy (Kreiker) published the excellent results obtained at the Eye Clinic of Debrecen.

This efficacious method was not widely used for various reasons, one being that the circulation of my paper was restricted during the second world war. The principal reason for its neglect, however, was Meisner's incorrect report in Thiel's " Ophthalmologische Operationslehre " (1942), vol. I. Although I had referred exactly to the chapter in question in Blaskovics and Kreiker's " Eingriffe am Auge " (2nd ed., 1945), Meisner's description of total hooding was not correct, and in consequence good results could not be obtained. Meisner says that in several cases in which total hooding had been carried out the ulcer had spread underneath the conjunctival flap. I can only reply that this happens very rarely indeed, and then only when the operation has not been performed in the right way. Kettesy (Kreiker) has not seen this complication in 56 cases, and I who have made more than a hundred total hoodings have seen it only in two very severe cases, both of them treated before the discovery of penicillin. The final results were evisceration in one case and a pea-sized staphyloma covered with conjunctiva in the other. Two losses only in so many cases prove that total hooding is an excellent method for healing one of the most malignant inflammations of the cornea.

Meisner obviously misunderstood the fundamental principle of total hooding when he reported that the sutures were knotted above the cornea. What he describes is not total hooding, but Kuhnt's double flap with all that operation's drawbacks, to which I shall later refer. The *punctum saliens* of total hooding is that by strongly anchoring the flap to the sclerotic below the limbus, we may gain time for the flap to adhere to the ulcer.

There is another reason why this method is not more popular: it is in strict contradiction to the classic principle of *ubi pus, ibi evacua*. I confess that I too was somewhat sceptical at first, and that I took great care to observe whether the good results were not due to some coincidence. But my experience during more than eight years has convinced me that total conjunctival hooding is the most efficacious method for the treatment of serpiginous ulcer.

Technique

After anaesthetizing with 1 per cent. pontocaine or 5 per cent. cocaine, the palpebral fissure is opened with Hess' or some other usual speculum. The bulbar conjunctiva is swelled by a 2 per cent. novocaine solution and then circumcised with Cooper's scissors along the limbus (Fig. 1). The circumcised conjunctiva is undermined as far as the upper fornix together with Tenon's capsule until the cornea can be covered by the prepared flap without tension. Then the conjunctiva under the limbus is pushed back so that the sclerotic below is bare to an extent of 3-4 mm. in breadth. With a fixation forceps of medium strength—in order to fix the bulbus—the inferior rectus is grasped, and with a convex knife incisions

2 mm. long and a quarter of the sclerotic deep are made at 4.30, 6, and 7.30 o'clock in the places designed for anchoring. For the sutures 5/0 catgut is used, first because it is soft and does not cut through the conjunctiva, secondly because

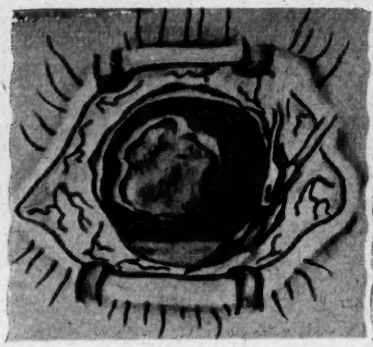

FIG. 1.—Circumcision of the raised bulbar conjunctiva in the limbus.

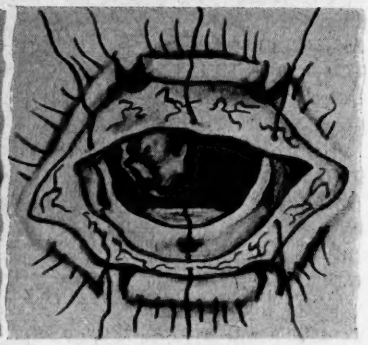

FIG. 2.—The prepared conjunctiva after insertion of the sutures. Anchoring in the sclerotic at 7.30, 6, and 4.30 o'clock.

it is resorbed and does not require removal. Thin silk or nylon sutures are quite suitable too. After the incision into the sclerotic, three sutures are inserted into the upper part of the flap about 2 mm. from the margin of the wound opposite the proposed anchoring. Then, grasping the muscle again, the sutures are anchored to the sclerotic through the wound in the prepared sclera. Suturing is continued through the conjunctiva so as to place the sutures at 2 mm. from the lower wound margin of the bulbar conjunctiva (Fig. 2). The sutures are then pushed aside and the ulcer is curetted with a fine Meyhöfer spoon in such a way as to remove the necrotic and disintegrated parts as far as possible. The undermined layer of the cornea covering the margin is dissected with fine scissors if necessary, and thus this part can also be cleaned. (With abscesses of the cornea the abscess must be opened first. After removal of the covering layer of cornea, the cavity is cleaned. The further treatment is the same as for serpiginous ulcer.) After removal of the ulcer the hood is closed with knotted sutures (Fig. 3). The first day the patient should be kept in bed and wear a binocular bandage, but from the second day onwards the operated eye is kept open.

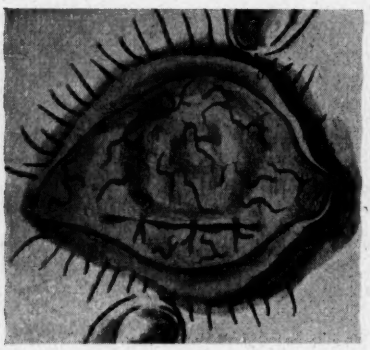

FIG. 3.—Total hooding completed. Sutures anchored in the sclerotic 2 mm. below the limbus.

Complications

Complications during the operation are rare. It may happen that there are scars on the conjunctiva owing to some previous

disease, so that it is difficult to draw down the flap. This can be dealt with by incisions into the upper part of the taut conjunctiva. It also occurs sometimes that the cornea—if very thin—is perforated during the operation, but this is not a serious disturbance. Since perforation generally occurs during the anchoring to the sclerotic, it is advisable to use very fine, thin needles. If, despite all precautionary measures, perforation occurs, the patient is kept in bed for a few days in order to promote the restoration of the chamber.

As Kettesy also affirms, the state of the patient usually shows a remarkable change even on the first day after the operation. The pains subside and the eye becomes quiet, so that special post-operative treatment is not necessary. But with grave ulcers this is not always the case and lately we have ensured the success of the operation by the administration of heteroprotein and penicillin which have proved very helpful in cases which threatened to become refractory. Mydriatics should always be given to keep the pupil dilated until complete recovery. Warm compresses of camomile infusion may be used to promote healing by hyperaemia.

Patients with a totally hooded serpiginous ulcer must remain in hospital for much shorter a time than those who are treated in the conservative way. Kettesy found that while the latter had to remain in hospital for an average of a fortnight, the former needed medical attendance for 6 days only. If we deduct the time necessary for the healing of the removed lacrimal sac and only consider the duration of medical attendance required for the healing of the hood, this may be reduced to 4 days. To these we must add the time which the patient has to spend in hospital after removal of the hood, because only then can we consider our therapy as complete. Kettesy says therefore that the average for medical attendance of a totally hooded serpiginous ulcer is seven days. This is just about half the time required for cases treated conservatively. Thus not only is the treatment shorter, but also the patients are able to return to work much sooner. Of course the cases we publish had to have longer medical attendance, because they were the gravest.

Removal of the Hooding.—Kettesy says that this may be done after six months. We believe, however, that it is not necessary to wait so long. If the eye is pale and quiet the hood can be safely removed 8 to 12 weeks after the operation. We must allow that much time at least for the filling of the corneal ulcer, for the removal of the destroyed cell débris, and for the strengthening of the new granulation tissue. When the hood was removed too early, we observed renewed inflammation and hypopyon in more than one case. We must assume that this was due to the fact that

strong chemotaxis sets in owing to the diffusion of toxins from the bacteria present as saprophytes in the conjunctival sac. These toxins penetrate through the area of the granulation tissue which is not yet sufficiently dense, having been bereft of its epithelium for formation of the hood. The time required for healing depends on the extent and depth of the ulcer. These factors must be considered individually in choosing the moment for removing the hood. But however long we wait, we have to be prepared for strong irritation in most cases when the ulcer has been very large. This keratitis is however responsive to heteroprotein and the usual local treatment.

After anaesthetization with 1 per cent. pontocaine or 5 per cent. cocaine the hood can be easily detached from the cornea with scissors, forceps, and keratome, as it adheres only to the site of the ulcer. After opening there remain about 3-4 mm. of superfluous conjunctiva. Before, this used to be cut. According to our new practice we shave off the superfluous conjunctiva from Tenon's capsule and separate it as far as the upper fornix in order to eliminate the shortening of the latter caused by the hood. The conjunctival flap which has been severed is pushed upwards until the margin of the superfluous part reaches the limbus. Then a doubly-armed suture is placed in the conjunctiva and the ends, having been passed through the corresponding places of the upper eye-lid, are knotted above the skin. On the next day the suture may be removed, because conjunctiva is firmly held in place by fibrin. Further treatment is that usually given for keratitis.

Case Reports

Case 1.—Sz. J., a peasant aged 66 years. His left eye had been painful for a week. He knew of no injury. He had not seen a doctor. Admitted June 2, 1945.

Diagnosis: ulcus serpens corneae cum hypopyo et dacryocystitis chronica l.s. Visual acuity right eye 5/5, left eye movements of hand.

Bacteriological report: pneumococcus.

For two days the usual local treatment was given (painting with $ZnSO_4$, 1 per cent., optochin, 10 per cent., argyrol, 0·02 per cent. scopolamine, 5 per cent. dionin drops). The lacrimal sac was immediately removed and the patient was given 0·1 cc. typhus vaccine (as heteroprotein) intravenously.

Temperature 103·1°F. But despite treatment progression continued. On June 5 we carried out a total hooding. The next day the eye was quiet and healed uneventfully in 10 days.

The patient returned after three months for opening of the hood with a pale and quiet eye. The removal of the hood presented no complications, and after the usual local treatment (scopolamine, dionin, argyrol and compresses) the patient recovered in six days. V.A. after removal of the hood, right eye 5/5; left eye, only movement of hand. We intended to carry out an optical iridectomy, but the patient never came back, although he was asked to do so.

Case 2.—V. J., a woman aged 50 years. Her left eye had been painful for a week. She had been once to see a doctor, who told her to go to hospital immediately, but she did not come until a week later. Her eye was in a very

grave state; the ulcer not only occupied three quarters of the cornea, but was also very deep. There was a hypoyon of about 4 mm. in the chamber. The lacrimal sacs were normal.

Bacteriological report: pneumococcus.

V.A. right eye 5/5; left eye, perception of light.

Hooding was carried out immediately. During the operation the very thin cornea became perforated. The next day the eye was fairly quiet, but for the sake of safety the patient was given a typhus injection of 0·1 cc. intravenously. Temperature 103·8°F. Because of the perforation the patient had to remain in bed for five days. Recovery was uneventful, and she left nine days after hooding.

The patient reported for opening three months later, with a perfectly quiet eye. The flap covered the cornea completely. Opening was normal. Afterwards a strong irritation—due to a large erosion—set in with a small hypopyon, which healed, however, in one week after administration of heteroprotein and local treatment. The patient's state is now V.A. right eye 5/5; left eye, movements of hand. We advised corneal transplantation, but she refused to have it performed.

Case 3.—T. F., a peasant aged 74, applied for admission on August 29, 1945, saying he had been having pains in his left eye for three days. He had not seen a doctor.

Diagnosis: Ulcus serpens corneae cum hypopyo et dacryocystitis chronica l.s. Cataracta progrediens o.d.

V.A. right eye 5/50, uncorrectable; left eye, movements of hand.

Bacteriological report: pneumococcus.

The lacrimal sac was immediately removed, and for a few days the usual conservative treatment was carried out, but the ulcer continued to grow. By September 2 the ulcer was of medium depth, undermined, its margin extending inwards. Total hooding was performed without any complications. The next day the eye was quiet and remained open. The usual treatment was given. On the third day the eye became slightly irritated and the flap began to swell, but after an injection of heteroprotein (temperature 102°F.) it healed within six days. About two weeks later the right eye was operated on for cataract with good result.

The patient did not return to hospital before the spring of 1948. After opening had been performed only a very fine scar was visible in place of the ulcer on the temporal side of the cornea. V.A. right eye, with adequate correction 5/8; left eye 5/20.

On June 14, 1949, patient came again, saying that his left eye was blind. Diagnosis: Cataracta totalis o.s. After operation for cataract V.A. left eye, with adequate correction, 5/15.

Case 4.—K. M., a quarryman 47 years old, applied for admission on May 7, 1947. His right eye had been injured by a stone splinter five days previously. He had been treated for two days by a doctor, who sent him to hospital when his condition deteriorated.

V.A. right eye 1/50; left eye 5/12, uncorrectable. The lacrimal sacs were normal.

Diagnosis: Ulcus serpens corneae cum hypopyo o.d., macula corneae o.s.

Bacteriological report: pneumococcus.

For two days the patient was given penicillin drops at intervals of 15 minutes in day time and 30 minutes at night (1 cc. 5,000 units) and heteroprotein (typhus vaccine which caused a temperature of 104°F.). Despite the treatment the ulcer continued to grow with only slightly diminished rapidity. As an experiment $10 \times 30{,}000$ units sodium penicillin were administered subconjunctivally within 24 hours, but hardly influenced the growth of the ulcer. After five days of more or less ineffective treatment with penicillin, a total hooding was successfully performed although the conjunctiva had become very irritated and friable. On the following day the eye was quiet and the pains had ceased. After the usual post-operative treatment the patient left hospital eight days later, having completely recovered.

He returned on February 26, 1948, for removal of the hood with a perfectly quiet eye. After an uneventful opening strong irritation set in which subsided,

however, after local treatment and administration of heteroprotein within seven days. His present condition is V.A. right eye 5/30, uncorrectable; left eye 5/12, uncorrectable.

Case 5.—*K. A.*, a locksmith 30 years old, was admited to hospital on September 18, 1947. While at work on September 9 his forehead had been severely injured by the recoiling arm of a crane. He had been treated for fractura baseos cranii at the surgical department of another hospital. According to the surgeons an ulcer had developed on the 3rd or 4th day of his unconsciousness (probably as a consequence of lagophthalmos) and was unresponsive to conservative treatment.

When the patient was admitted his left cornea showed a medium deep ulcer the size of a large lentil at 6 o'clock, with a necrotic floor, of yellowish-white colour, with a typical progressing margin and a hypopyon of about 2 mm. The lacrimal sacs were normal.

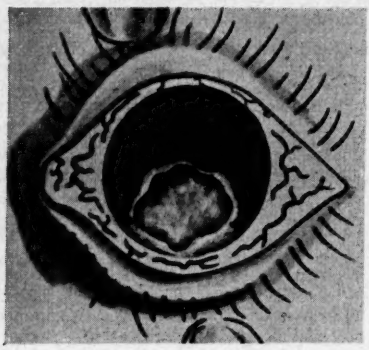

FIG. 4 (*a*).—Case 5, left eye, showing ulcer before hooding (Oct. 1947).

V.A. right eye 5/5; left eye hand movements.

Diagnosis: ulcus serpens corneae cum hypopyo o.s.

Bacteriological report: pneumococcus.

The ulcer was painted with 20 per cent. $ZnSO_4$ once, and besides the usual local treatment the patient was given penicillin drops (1 cc. 5,000 units) at intervals of 15 minutes during the day and 30 minutes at night for three days. This treatment was combined with subconjunctival administration of sodium penicillin (10 × 30,000 units in 24 hours), further 8 × 2 sulphonamide tablets daily and once 0·1 cc. typhus vaccine intravenously. (Temperature 103·8°F.) Despite this energetic treatment the ulcer continued to grow slowly but steadily, see Fig. 4 (*a*). As conservative treatment had no success, a total hooding was performed, which healed well in six days after the usual post-operative treatment.

The patient did not report for opening of the hood until April 26, 1948, see Fig. 4 (*b*). After an uneventful operation strong irritation set in which was controlled in eight days by local treatment and the administration of heteroprotein.

FIG. 4 (*b*).—Case 5, left eye, 7 months after hooding, before removal of the hood (April 1948).

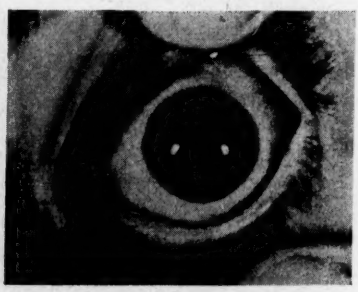

FIG. 4 (*c*).—Case 5, left eye after removal of hood, cornea entirely healed. Fine, clearly defined scar in place of the ulcer.

His present condition is V.A. right eye 5/5; left eye 5/15, uncorrectable, see Fig. 4 (*c*).

Case 6.—B. F., a peasant aged 82, was admitted to hospital with a diagnosis of ulcus serpens corneae cum hypopyo o.d. on July 30, 1947. He said that his right eye had been injured by the thorn of an acacia tree five days previously. The doctor who had treated him had sent him to hospital as his condition deteriorated. There was a typical, not only superficial, but deep serpiginous ulcer with a hypopyon of 2-3 mm.

V.A. right eye, hand movements; left eye 5/8.

Bacteriological report: pneumococcus.

We began by trying penicillin treatment. The patient was given sodium penicillin drops at intervals of 15 minutes in the day and 30 minutes at night (1 cc. 5,000 units). Simultaneously he received 10 × 30,000 units penicillin subconjunctivally within 24 hours. But the ulcer continued to grow. On August 2 a total hooding was performed. The next day the eye was slightly still irritated. The patient was given 200,000 units sodium penicillin and one injection of heteroprotein intramuscularly within 24 hours. (Temperature 102·2°F.) After this treatment, complete healing occurred in six days.

The patient returned in July, 1948, for removal of the hood. After an uneventful operation he left hospital five days later.

He returned in three months for an optical iridectomy, and after this had been successfully performed in the nasal direction the V.A. right eye 5/15; left eye 5/8.

Case 7.—N. J., a woman aged 64, was admitted to hospital on June 4, 1948. She said that ten days previously her eye had been injured by the branch of a shrub. She had not seen a doctor.

Diagnosis: Ulcus serpens corneae cum hypopyo et dacryocystitis chr.l.s.

Bacteriological report: pneumococcus.

There was an extremely large ulcer with a small deccemetocele in the centre and a small hypopyon. V.A. right eye 5/5; left eye, perception of light. The ulcer was immediately hooded. On the following day the eye was perfectly quiet, so that besides the usual local treatment only typhus vaccine was given intravenously once (temperature 102·2°F.) in order to promote healing. The patient left hospital seven days later.

She returned to have the hood removed on October 27, 1948, the whole cornea being covered by the flap. There was no complications after the removal of the hood and she left hospital eight days later, completely cured. At present only fine, diffuse scars are visible on the cornea. V.A. right eye 5/5; left eye 5/50, uncorrectable.

Case 8.—E. J., a man aged 28, a carpenter, applied for admission on August 15, 1948. His left eye had been painful for ten days and he had been treated by a doctor. In the centre of his left cornea there was a deep serpiginous ulcer surrounded by a large halo. The ulcer perforated while being examined. The lacrimal sacs were normal.

Diagnosis: ulcus serpens perforans corneae cum hypopyo o.s.

Bacteriological report: pneumococcus.

V.A. right eye 5/5; left eye, perception of light.

The ulcer was immediately hooded. There was an uneventful healing within six days.

Removal of the hood was performed three months later. After the operation considerable irritation set in, which subsided, however, after the usual treatment in ten days. Control June 17, 1949. The centre of the cornea shows a thick leucoma, while the marginal parts are quite clear. In Autumn a keratoplasty which seems very promising in this case will be performed.

Case 9.—Sz. J., a woman aged 56, attended hospital on July 12, 1948. She said that three days previously a cow had hit her left eye with its tail. On the

following day her eye began to hurt and she went to see a doctor, who sent her to hospital.

Diagnosis: ulcus serpens corneae cum hypopyo o.s. The lacrimal sacs were normal.

Bacteriological report: pneumococcus.

V.A. right eye 5/5; left eye, only hand movements.

Hooding was carried out immediately. The next day the eye was slightly irritated still, so $10 \times 20{,}000$ units sodium penicillin were given intramuscularly in 24 hours. The eye healed in ten days.

Four months later the patient came to have the hood removed. The eye was quiet and showed a translucent flap, which entirely covered the cornea. The patient left hospital seven days later. Control on March 10, 1949. V.A. right eye 5/5; left eye 2/50, uncorrectable. We advised optical iridectomy.

Case 10.—K. J., a woman aged 75, was admitted to hospital on September 1, 1948. She had already been treated as an out-patient for a refractory ulcer on the temporal side of the left cornea, which had healed after conservative treatment, forming a medium thick scar. About a month later the patient reported again, saying that her eye had been painful for the last three days.

Diagnosis: ulcus serpens corneae cum hypopyo o.s.

Bacteriological report: pneumococcus. The lacrimal sacs were normal.

A total hooding was performed immediately. After the operation strong irritation set in. $10 \times 20{,}000$ units penicillin were given intramuscularly in 24 hours, as well as heteroprotein every second day. The irritation subsided very slowly. On the 5th day the flap began to slip upwards, but it stopped at about 2 mm. from the lower margin of the cornea. The patient left hospital after a stay of two weeks.

She returned for removal of the hood on January 30, 1949. After an uneventful operation and the usual post-operative treatment she left hospital eight days later. Control on June 25, 1949, V.A. right eye 5/6; left eye, hand movements (Cataracta totalis).

Case 11.—N. J., a peasant aged 74, admitted to hospital on September 14, 1948.

Diagnosis: ulcus serpens corneae cum hypopyo et dacryocystitis chr.l.d. Xerophthalmos l.s.

The patient stated that the left side of his face had been wounded by a shot in the first world war. Since then his left eye had been blind. His right eye

FIG. 5 (*a*).—Case 11, severe serpiginous ulcer in right eye, xerophthalmos in left eye.

had been injured three days previously by a splinter of wood. He had not consulted a doctor. For the last 24 hours his right eye had been blind, too. (Fig. 5 (*a*).)

FIG. 5 (*b*).—Case 11, right eye, 3 months after hooding, before removal of the hood.

Bacteriological report: pneumococcus.

V.A. right eye, perception of light; left eye, no perception of light.

Total hooding was performed at once and the diseased lacrimal sacs removed. On the following day the eye was perfectly quiet and it healed in twelve days of local treatment.

The patient came on December 12, 1948, to have the hood removed. His cornea was entirely covered by a pale and translucent conjunctiva. (Fig. 5 (*b*).) After removal of the hood and the usual local treatment the patient was healed in seven days. Control June 3, 1949. The cornea showed a dense scar the size of a pin head, surrounded by fine diffuse cicatrization. (Fig. 5 (*c*).) V.A. right eye 5/25, uncorrectable; left eye, no perception of light.

FIG. 5 (*c*).—Case 11, right eye, showing cornea healed, after removal of hood.

Discussion

We can only publish cases treated since the summer of 1945, as the material collected before then was destroyed during the war. We had to make drawings of the first serpiginous ulcers treated with total hooding as we were unable to procure a camera before the spring of 1948. Most of the cases were first treated conservatively, and only when this was of no avail did we resort to total hooding. In a few severe cases, however, hooding had to be performed immediately, so as not to lose a minute in saving the cornea from destruction.

Penicillin.—It is only since 1947 that we have been able to use penicillin. First we administered it intramuscularly without any result whatever; later we instilled drops of a solution of 5,000 units to 1 cc. into the conjunctival sac at intervals of 15 minutes during the day and 30 minutes at night. With incipient serpiginous

ulcers this method yielded good results. Of course we tried to increase this good effect by adding dionin and heteroprotein. But as in grave cases this method was not successful either, we tried subconjunctival administration, injecting 10 × 20,000 to 30,000 units of penicillin dissolved in 1 cc. 0·9 per cent. sodium solution (that is 200,000 to 300,000 units) daily. But as these injections were very painful, the solution being hypertonic, we added 0·4 cc. 4 per cent. novocaine solution which contained 0·00004 gr. adrenalin in 1 cc. After the subconjunctival injections of penicillin, the patients always complained of severe pains as soon as the effect of novocaine had ceased, owing to the irritation of the tissues caused by the hypertonic solution. The bulbar conjunctiva became more swollen, hyperaemic, and friable. More unpleasant than all this, however, was the fact that no result was obtained.

In the course of our examinations we soon discovered that with severe serpiginous ulcers penicillin given subconjunctivally was not only of no avail, but also impaired the chances of total hooding on account of the changes in the conjunctiva mentioned above. Grignolo and Bruna (1947) who have made a special study of penicillin treatment of serpiginous ulcers have also found that while it was efficacious in mild cases, it had no effect in medium severe and severe cases, by whatever route it was given. Recently Sorsby and Ungar (1948) have given rabbits 1,000,000 units crystalline penicillin sub-conjunctivally in 48 hours. In further experiments one injection of 500,000 units was given with satisfactory results. In a few cases of serpiginous ulcers they injected 200,000 to 500,000 units sub-conjunctivally into human eyes and their results were distinctly promising. It is certain that some cases of incipient or medium severe serpiginous ulcer are responsive to large amounts of penicillin administered subconjunctivally. But the examinations of Grignolo and Bruna as well as our own proved that in the majority of severe cases penicillin was of no avail however it was administered.

We can assume that the reasons for this failure were these. A certain quantity of penicillin which is to be considered as crystaloid can reach the blood stream in the sense of Donnan's equilibrium by the arterial part of the capillaries of the marginal network, through the endothel walls of the arteries. The penicillin which has thus penetrated into the capillary system prolongs the eliminating circumstances of the capillary loops by changing the colloid-osmotic pressure. Owing to the altered osmotic pressure a great part of the penicillin is further eliminated in the lower parts of the capillaries and reaches the cornea with the lymph. It may be assumed that penicillin given subconjunctivally acts as a hypertonic solution and increases the level of penicillin in the

cornea by changing the osmotic pressure in the conjunctival tissues. The circulation of lymph in the cornea being strongly hindered when large ulcers are present, the quantity of penicillin is necessarily reduced. This probably explains the fact that we were not successful when we treated severe serpiginous ulcers with subconjunctival injections of penicillin. The greater part of penicillin given subconjunctivally reaches the blood stream through the venous resorbing part of the capillary system, and leaves the conjunctiva in a centripetal direction and highly diluted. The lymph in the tissues also carry away the penicillin from the conjunctiva.

As regards the effect of penicillin administered retrobulbarly (500,000 units), it can only be explained by its being resorbed by the veins and the lymphatic system, thus being transferred to the blood stream and into the cornea. This also happens with penicillin given intramuscularly, which does not yield satisfactory results in cases of serpiginous ulcers. Since in severe cases of serpiginous ulcers every minute counts because of their rapid growth, we believe it is useless to resort to a method which is in contradiction to the present anatomical and physiological views.

When the eye became irritated after total hooding we gave penicillin intramuscularly because the conjunctival flap is enlarged and new, and it seems possible to transfer penicillin in adequate concentration to the ulcer through the veins growing into it, and so to promote the healing effect of the hood. It is certain that in some cases irritation was controlled by this treatment and that healing proceeded without complications. (It is true, however, that before the discovery of penicillin, post-operative irritation was sometimes responsive to heteroprotein and local treatment.) We are studying this question which seems theoretically plausible, and if it be possible to transfer adequate quantities of penicillin into the corneal ulcer, we shall use this therapy regularly after every total conjunctival hooding.

Reasons for the Healing Effect of Total Conjunctival Hooding.

(1) By " anchoring " the conjunctiva to the sclerotic, which is the punctum saliens of this operation, we give the veins enough time to eliminate the débris of the corneal ulcer, to clear the latter, and to ensure a firm coalescence between flap and ulcer. The drawback of Kuhnt-Brückner's flap is that it retracts too quickly, generally before this coalescence could have taken place. Therefore Meisner (1942) is also incorrect in that he placed the suture above the cornea, where " anchoring " is impossible; the illustration he published as " total hooding " is just Kuhnt's double flap above the cornea.

(2) Through the veins of the flap, masses of white blood cells rapidly invade the infected site and so the fight against the pneumococci becomes not only possible, but effective.

(3) The bacteriostatic effect of the cellular fluids emerging from the surface of the wound in the flap also promotes healing.

(4) The temperature in the covered cornea rises. This also has a healing effect due to the accelerated metabolism of the cornea.

(5) Besides increased metabolism, mitosis of the corneal cells is stimulated on the one hand and masses of fibroblasts grow into the ulcer and fill it out on the other.

(6) By total hooding winking of the eyelids which irritates the diseased cornea is eliminated.

(7) Total hooding prevents a new infection by bacteria from the cornea.

Before total hooding was carried out, healed serpiginous ulcers left thick, large, and sometimes ectatic scars, while after total hooding scars are remarkably fine. Thicker leukomata with a clearly defined margin were only present when the ulcer had undermined the cornea to a high degree. The scars occurring after total hooding can be treated with optical iridectomy or corneal transplantation. In several cases which seemed absolutely hopeless satisfactory visual acuity could later be obtained in this way.

Our results are all the more valuable because in over half our cases successful operations were performed on patients of more than 60 years of age. It is well known that while the prognosis in cases of serpiginous ulcer is fairly good with young people, it is poor in old age.

It is interesting that the lacrimal sac was diseased only in four out of the eleven severe cases we published and that this percentage is to be found in almost all the cases of serpiginous ulcer.

Most cases of serpiginous ulcer occur in summer or in early autumn. I believe we are right in assuming that this is not only because of accidents due to agricultural work (injuries caused by cornstalks, wheat ears, maize leaves, etc.); these are undoubtedly important among the causes of serpiginous ulcers, but we must also bear in mind that the virulence of pneumococci in the conjunctiva is intensified by heat so that this disease is more frequent in warm weather. We believe that for this reason severe cases of serpiginous ulcer are rare in western countries with a cooler climate (*e.g.*, in Switzerland, according to Brückner, 1949). A certain time is necessary for the development of the severe type, which depends on the virulence of the pneumococci and the resistance of the cornea. From the literary data we can conclude that in countries

with a cooler climate the progression of the disease is less rapid, the pneumococci being less virulent. The degree of civilization in various countries is important too. In countries where the population is enlightened enough to ask for medical advice at once, the disease can be treated by a specialist in the incipient stage, so that neglected cases are very rare.

If a serpiginous ulcer is to be treated successfully it is necessary for the patient to see a specialist as soon a possible. While incipient ulcers heal without complications — *restitutio ad integrum*—great difficulties arise when ulcers have to be dealt with at a later stage. A strong deterioration of visual acuity is always to be expected because of postoperative corneal scars which permanently impair the patient's working ability. Stein is right in saying that this part of the question can be solved by efficient work on the part of the general practitioner.

Another important factor is general popular enlightenment and—last but not least—social insurance for everybody, so that material considerations can no longer prevent patients from going to hospital in time.

Correct Therapy.—When the ulcer is small, conservative treatment should always be resorted to first; this is, local treatment (painting with 20 per cent. $ZnSO_4$, dionin, instillation of penicillin drops at intervals of 15 to 30 minutes, mydriatics) and typhus vaccine as heteroprotein administered intravenously. If all this does not prevent aggression of the ulcer, or if the ulcer is already extensive (especially when situated in the centre) total hooding should be performed without delay.

Summary

We consider total conjunctival hooding the most efficacious method for healing serpiginous ulcers. This is proved by more than 150 successful operations, including the cases already published by Kettesy. In the incipient or medium severe stage of the disease the usual conservative treatment ought always to be attempted, and only when this is not successful should hooding be performed. In severe cases, hooding should be carried out immediately so as to prevent further losses. Our experience has shown that with grave ulcers the effect of penicillin is not satisfactory by whatever route it may be administered. It may, however, promote healing when given intramuscularly after total hooding.

To ensure full success of total hooding it is essential to prevent traction of the conjunctival flap, and to "anchor" the latter to the sclerotic in three places 2 mm. below the limbus.

The hood should only be removed when the eye is absolutely quiet and pale. This depends on the gravity of the ulcer and generally takes 2 to 3 months.

After total hooding the patients need not remain in hospital as long as when they are treated in the conservative way; thus they can return to work after much shorter a time. Visual acuity is much better after total hooding and final invalidity is also considerably reduced.

We have been performing total hooding for more than eight years and only two out of all our cases were lost. Therefore we think that this method should be used frequently, not only in cases of serpiginous ulcers, but in all cases of serious corneal ulcers.

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A SIMPLE MANOMETER FOR THE CONTINUOUS MEASUREMENT OF INTRA-OCULAR PRESSURE*

BY

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THE adequate measurement of the intra-ocular pressure, both clinically and experimentally, has remained a baffling problem. The tonometer has obvious disadvantages which have been summarized by Duke-Elder (1932). Chief amongst these, in the opinion of the present authors, is the possibility of self-deception, since the variations in the results of repeated determinations are often quite large and there is always a danger that the investigator will choose unconsciously the value expected. Manometric methods involve the insertion of a needle into the anterior chamber; this of itself may upset the normal physiology of the eye, although unequivocal evidence that it does so is lacking. Moreover the investigator is ignorant of the pressure within the eye before inserting the needle, so that to prevent loss or gain of fluid by the eye, he must arbitrarily choose a certain pressure of saline within the needle to minimize these changes An incorrect choice may disturb the normal mechanism of production and drainage of aqueous humour, and there is thus some uncertainty regarding the physiological condition of the eye on this count and greater uncertainty regarding the true value of the intra-ocular pressure in the eye before the needle was inserted, since the pressure imposed on the eye by the saline in the needle may persist for some time. Again, the mechanical registration of changes in the intra-ocular pressure requires that fluids either leave the eye or enter it; this may be largely cut down by a compensatory device in which the excursions of a minute bubble of air in the recording system are kept to a minimum; the operation of such a compensator is, however, tiresome, and a membrane-type manometer, in which very small changes in the volume of fluid in the system are magnified into large excursions of a reflected beam of light, is preferable. The instrument to be described here is of this type and gives a deflection of some 3 to 4 in. of a light spot on a scale, 5 feet away, in response to a rise in pressure of 10 cm. H_2O; the fluid loss involved in this reflection is only 8 mm. corresponding to some 2 to 3 minutes' production of aqueous humour if present estimates of this rate are acceptable; it is sufficiently sensitive to show the normal pulsation corresponding to the arterial systole.

* Received for publication November 4, 1949.

Apparatus

Fig. 1 illustrates the manometer itself, which consists of a piece of pyrex glass tubing approximately 45 mm. long by 7 mm. in diameter, worked to a lip (A) at one end and ground to fit an ordinary record-type hypodermic needle at the other end (B). A No. 15 needle is removed from its brass base by the application of heat to the soldered joint and is re-soldered into a brass adaptor made to fit a length of polythene tubing. The end of the brass holder from which the needle was removed is turned down for a few mm. of its length so that it may also fit the polythene tubing. A tap (T) is fitted into a length of 3 mm. pyrex glass tubing, one end of which pierces the 7 mm. tube, while the other end is drawn out slightly for union with a length of small diameter rubber tubing.

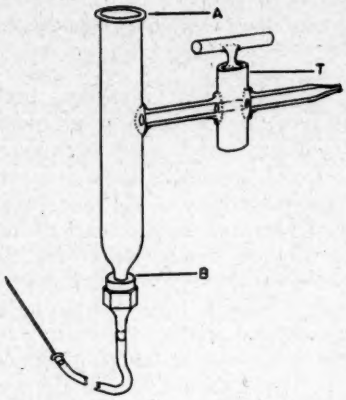

FIG. 1.—Construction of manometer.

Fig. 2 illustrates the frame, which has an over-all length of 30 mm. and carries at one end a clamp (C) capable of gripping the manometer rigidly in any position along its length; the other end is bent through 90° and filed out to form two diverging rods 2 mm. square (X, X). The inset to Fig. 2 shows a light brass carrier soldered to the centre of a short length of watch hair-spring (S) which is soldered in turn, under slight tension, between the 2 mm. rods (X, X) at the end of the frame, in such a way as to bring the mirror (M_1) a little below and at an angle to the top of the frame when the spring (S) is at rest. (R) is a perspex roller, 3 mm. in diameter and 4 mm. in length; it is mounted between two small projections on the carrier, and should turn very freely on its axle. M_2 is a small reference mirror of the same dimensions as M_1, mounted on a

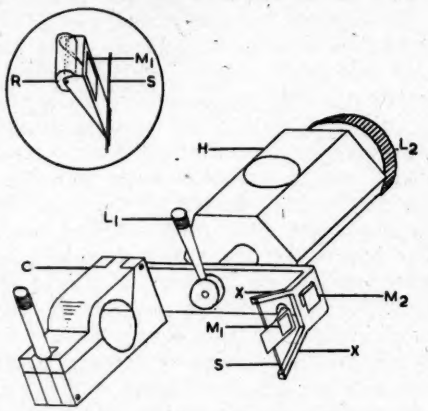

FIG. 2.—Frame with clamp and arrangement of mirrors.

small piece of brass foil soldered to the frame. L_1 is a locking device which, when released, allows the frame to be tilted a few degrees in relation to its mounting block (H), which may, in turn, be rotated around or raised upon a vertical rod, and locked in position by L_2.

Fig. 3 shows the manometer in its frame, P being a thin latex rubber membrane tied with a silk thread over the lip end of the manometer. The carrier (Fig. 2, inset) is of such dimensions that the perspex roller (R) makes contact with the

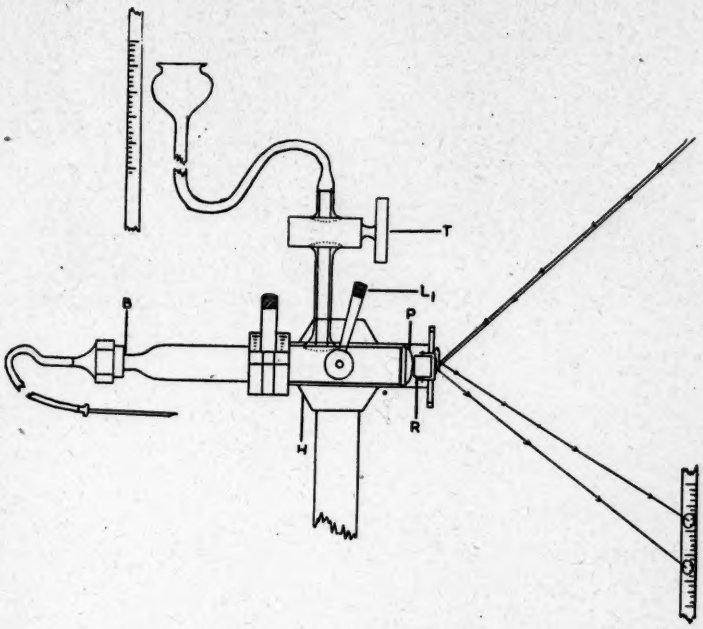

FIG. 3.—Manometer set up in frame.

centre of the membrane. A parallel beam of light is reflected off the two mirrors (M_1 and M_2) to give two spots on a suitably placed scale. The foil mounting of M_2 may have to be bent slightly to bring the reflections into close proximity. Any adjustment for height or direction may be carried out by releasing the locks (L_1 and L_2). The whole apparatus is filled with normal saline through the reservoir.

Fig. 4 shows the general arrangement for a set-up with two manometers.

Calibration.—With the needle inserted into a rubber bung and the tap open, the reservoir is raised to varying heights and the scale deflections recorded.

Measurement of Intra-Ocular Pressure. — With the level in the reservoir some 30 cm. above the level of the eye, the tap is turned

FIG. 4—Two manometers set up for use.

on so as to give a continuous drip; the superior rectus is gripped firmly and the needle inserted near the limbus; the tap is closed and, from then on, readings of the spot on the scale are made at intervals of a few minutes or less.

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THE EFFECT OF INTRAVENOUS INFUSION OF HYPERTONIC SALINE ON THE INTRA-OCULAR PRESSURE*

BY

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THE exchange of water between blood and eye fluids is very rapid (Kinsey, Grant, and Cogan, 1942) in comparison with the migration of sodium chloride across the blood aqueous barrier. Consequently, on making the blood hypertonic by the intravenous injection of sodium chloride, water should be withdrawn from the eye, and the intra-ocular pressure lowered. Qualitatively, such an effect has been described (Duke-Elder, 1926), and the observation has been cited as evidence in favour of the dialysis theory of the formation of the intra-ocular fluid, although an alternative interpretation was placed on the results by Robertson (1937). For

TABLE

Effect of Intravenous Infusion of 4·5 per cent. NaCl Solution on Intra-Ocular Pressure

No. of Experiments	Concentration of Na (mmols/kg.H_2O)				Fall in pressure (mm. Hg)	Rate of injection (ml./min.)
	B_1	B_2	Aq	r		
1	158	173	156	1·11	7·5	2·4
2	158	188	163	1·15	9	2·8
3	160	170	153	1·11	3·5	1·4
4	165	198	—	—	12·5	1·5
5	157	175	151	1·15	2	1·4
6	159	191	—	—	6	2·9
7	162	174	163	1·07	7·5	1·6
8	158	174	161	1·08	2	2·2
9	157	171	154	1·11	8	1·7
10	161	178	156	1·14	2	2·4
11	160	170	156	1·09	6·5	1·7
Mean	159	178	157	1·11	6	2

B_1, B_2 blood samples taken at beginning and end of experiment.
r = ratio (Concentration of Sodium in Plasma/Concentration of Sodium in Aqueous) at end of experiment.

a full understanding of the effects of hypertonic solutions on the intra-ocular pressure, however, it is not sufficient to give a single massive injection and observe the results; interpretation of any

* Received for publication February 10, 1950.

effects observed will be obscured by ignorance of the actual concentration of salt in the blood at any moment, owing to its elimination by the kidneys. In the present work, the concentration of NaCl in the blood has been raised gradually and continuously by an intravenous drip technique, and its value estimated at appropriate intervals; the concentration in the aqueous humour was determined, moreover, at the end of the period of measurement.

Experimental Procedure

Cats were anaesthetized with nembutal and one femoral artery and vein cannulated. After inserting the manometer needle into one eye, and waiting for the intra-ocular pressure to settle down to a reasonably constant value, 4·5 per cent. sodium chloride was infused into the femoral vein at a steady and predetermined rate (1·6 to 2·5 ml./min.). Blood samples were withdrawn from the femoral artery before and during the infusing of sodium chloride; at the end of the experiment, aqueous humour was withdrawn from the other eye at the same time as the sample of blood. Sodium was determined by methods already described (Davson, 1939); intra-ocular pressure by the manometer recently described (Davson and Purvis, 1950).

Results

In general, hypertonic saline produced a slow decline of intra-ocular pressure varying in extent from 2 to 12·5 mm. Hg, with a mean value of 6 (see Table). Fig. 1 illustrates a typical curve, whilst Fig. 2 is a mean curve computed from eleven experiments; it will be seen that the rate of fall in pressure slackens off very considerably, so that after about 20 min. of injection the pressure becomes virtually constant. Fig. 3 shows the results of an experiment in which the infusion ceased after about 30 min., but in which the intra-ocular pressure was recorded for a further 30 min. It will be noted that the pressure remained low and showed no sign of returning to its original value. This is typical of practically all the results in which the intra-ocular pressure has been followed for some time after the infusion ceased. The figures on the curves indicate the concentration of sodium in the plasma in mmols/kg. H_2O; the results, and others not presented here, show that the concentration of sodium rises continuously during the infusion. The relative concentrations of sodium in blood and aqueous at the end of the experiment indicated, moreover, that there was a considerable excess of sodium in the blood over that in the aqueous. Thus the normal ratio of the concentrations is about 1·04, whereas the ratio was never less than 1·07,

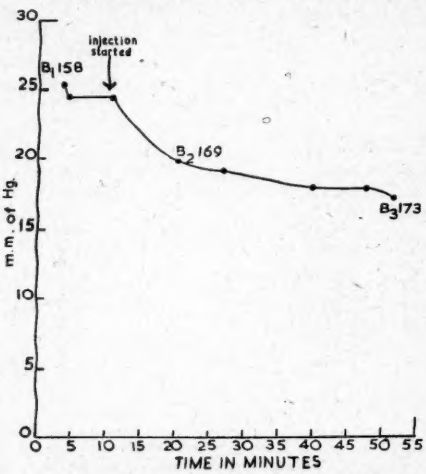

FIG. 1. Effect of intravenous infusion of hypertonic saline on intra-ocular pressure. Figures on curve indicate concentration of sodium in plasma in mmols/kg. H_2O.

and had an average value of 1·11. As a control, several experiments were carried out with isotonic sodium chloride; in general this resulted in a small rise in pressure, although in two experiments there was no change. The rise was probably due to the increased blood volume (Duke-Elder, 1926).

Discussion

The results leave one in little doubt as to the possibility of modifying the intra-ocular pressure by purely osmotic means; some quantitative considerations reveal, however, that the final result on the intra-ocular pressure is determined by a balance of osmotic withdrawal of fluid and secretory formation. Thus, on a dialysis or ultrafiltration theory, the only force available to drive fluid into the intra-ocular cavities is the difference between the intra-ocular capillary pressure and the colloid osmotic pressure of the plasma proteins. The maximal capillary pressure is unlikely to be more than 60 mm. Hg, whilst the colloid osmotic pressure is in the region of 25 mm. Hg; consequently, the maximal driving force is of the order of 35 mm. Hg. In the experiment illustrated in Fig. 1, the sodium ratio was 1.11, whilst the pressure was constant at some 17 to 18 mm. Hg, so that the difference of osmotic pressure draining water out of the eye was in the region of 380 mm. Hg. On the basis of the dialysis or ultra-filtration theory, therefore, the intra-ocular pressure should have been strongly negative. If, however, we assume a continuous formation of intra-ocular fluid by a secretory process, the withdrawal of fluid by osmotic means need not necessarily reduce the intra-ocular pressure by a large amount, the osmotic withdrawal being in some measure compensated by the continuous inward flow. Thus it is now well established that there is normally a continuous flow of fluid into the intra-ocular cavities, inwards by way of the ciliary body, and outwards at the angle of the anterior chamber. The intra-ocular pressure represents the balance struck between inward and outward

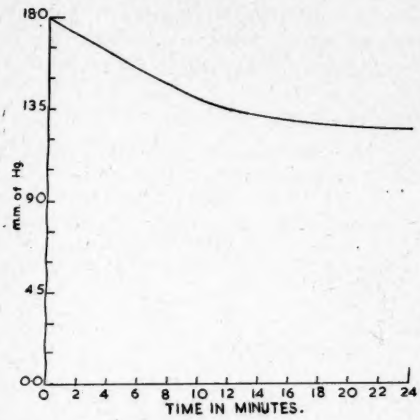

FIG. 2.—Effect of intravenous infusion of hypertonic saline on intra-ocular pressure, mean curve for 11 experiments.

flow. If an artificial outward flow is induced by the osmotic withdrawal of water, this effect will be balanced partly, if not completely, by the cessation of the normal drainage process; it is possible also, but not proved, that the fall of intra-ocular pressure, resulting from too great a loss of fluid, may be compensated by an increased rate of formation. The achievement of a steady state as indicated in Fig. 1, is therefore intelligible. We may note also that a further stabilization factor is the tendency of the concentration of sodium in blood and aqueous to become equal as a result

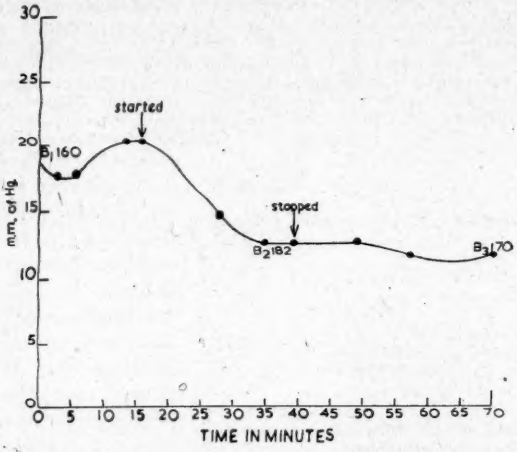

FIG. 3.—Effect of intravenous infusion of hypertonic saline on intra-ocular pressure, showing course of intra-ocular pressure after cessation of infusion.

of withdrawal of water from the aqueous humour. The results show, however, that they never did become constant, so that in our experiments there must always have been an osmotic withdrawal.

The clinical use of a single massive injection of hypertonic saline to reduce the intra-ocular pressure probably has its basis in the small fall in the intra-ocular pressure recorded here, although other factors may play a part. In several experiments on humans carried out during this work, chemical analysis revealed a definite increase in blood sodium (from 1 to 4 per cent.) after an injection of 20 to 30 ml. 30 per cent. NaCl. The intra-ocular pressure fell on the average by 8 mm. Hg Schiötz for about 1 hour. Simultaneous observations of the aqueous veins,

however, failed to reveal any striking change; it was thought that the osmotic drainage would cut down the normal drainage by these channels, but no evidence in the form of an unequivocal decrease in flow of aqueous was obtained.

Summary

Continuous intravenous infusion of hypertonic NaCl caused a small fall in the intra-ocular pressure, after which the latter was generally stabilized. Chemical analysis revealed that during the whole of the experiments there was a considerable excess of sodium in the plasma over that in the aqueous humour, the level in the blood rising continuously during the infusion.

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INTRA-EPITHELIAL EPITHELIOMA OF THE CONJUNCTIVA AND THE CORNEA (BOWEN'S DISEASE) HEALED BY CONTACT RADIOTHERAPY*

BY

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APART from the classical epitheliomata of the bulbar conjunctiva, whether epidermoid or not, attention should be drawn to the intra-epithelial epitheliomata, observed by Bowen since 1912 on the level of the skin and also since observed on the level of the mucous membranes.

McGavic (1942) reported five observations of this type of malignant tumour on the level of the conjunctiva and the cornea. Other cases have been described by Wise (1943), Khanolkar (1946), and Esterman, Laval, and Okrainetz (1947).

This tumour is characterized by a proliferation of epithelial cells within the epithelium itself, there being no perforation of the basal membrane, at least until a long time has elapsed, no invasion of the neighbouring tissues, and no formation of metastases.

The treatment of epibulbar epitheliomata, no matter what the anatomo-pathological type may be, is reputed to be very disappointing. *X* rays (Heckel, 1922) and radium (Mattice, 1914; Collins, 1915; Rados and Schinz, 1922) have met with notorious failure. Local excision as well as electrocoagulation is very often followed by a relapse. This is why most authors, including Duke-Elder (1946) and Mérigot de Treigny (1939), do not hesitate to resort to drastic measures and advise enucleation of the eye-ball or even exenteration of the orbit, if the lesions are very extensive.

We had the opportunity to observe an intra-epithelial epithelioma of the conjunctiva and the cornea which we were able to heal completely and without sequelae by contact radiotherapy. This success beyond expectation encouraged us to publish our observation, as, the effectiveness of this treatment being confirmed, the prognosis of epibulbar epitheliomata will be wholly modified.

Case History

On May 18, 1949, a 57-year-old man came to ask advice about a "spot" on the right eye-ball. This "spot" which had first appeared a year before, had started as a little reddish point, which gradually increased as time went on.

* Received for publication February 6, 1950.

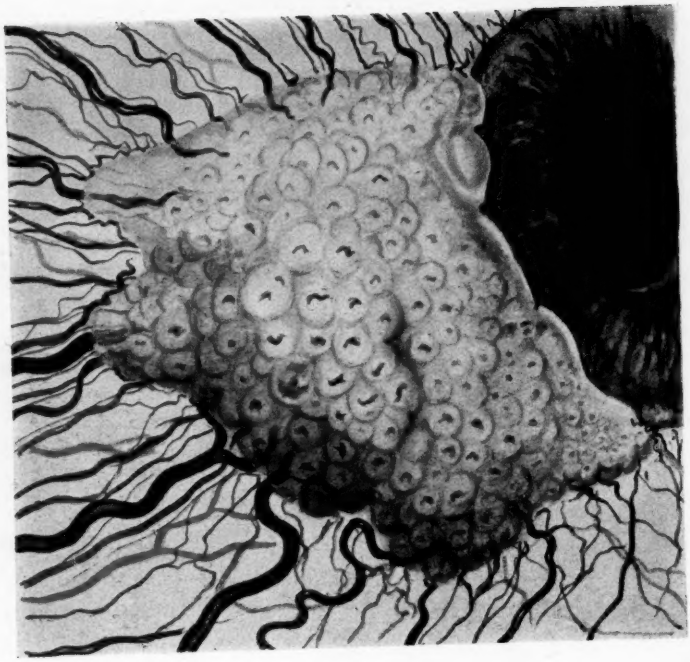

FIG. 2.—×5.

On the level of the paralimbic and infero-external part of the bulbar conjunctiva, a tumour formation was observed, extending from 7 o'clock to 10 o'clock (Fig. 1). It encroached by at least 1 mm. upon the cornea and was 5 mm. broad and 8 mm. high. Its edges were distinctly marked but a little irregular. Whitish in colour, it showed a granulated, uneven, rather gleaming surface. It did not adhere to the sclerotic and was slightly mobile. Though plainly protruding, it was not very thick (2 mm.) and was of rather firm consistency. On the conjunctival side of the tumour were to be seen some more or less turgescent blood vessels, which give to this area an appearance of very localized hyperaemia: this was not characterized by a diffused redness, but was caused by the presence of some broad, winding veins, which disappeared on the level of the tumour, as they penetrated into it. On the level of the limbus, at 9 o'clock a small and greyer spot was to be seen.

FIG 1.—May 18, 1949.

In the biomicroscope (Fig. 2) it could be seen that this spot was essentially composed of an accumulation of many little follicles, more or less regular, juxtaposed in mosaic, white in colour, and centred by a small vascular handle.

Apart from this, the eye presented no anomaly and vision was 10/10.

The left eye was anatomically and functionally normal. Our patient had never been ill, apart from operations for two hernias. He had two daughters, one of 13 years, the other of 16, both in good health. The mother had never had a miscarriage.

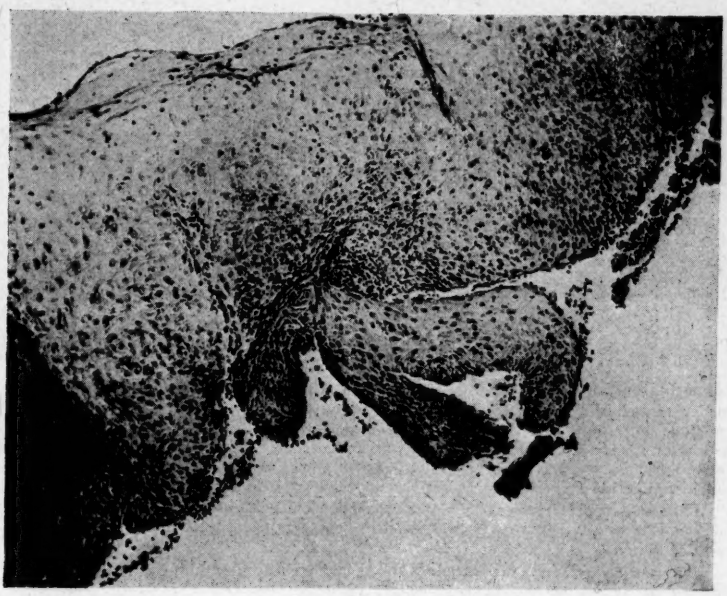

FIG. 3.—×140.

Further Examination.—A tumour fragment was excised for microscopic examination; it was easily disjoined from the deep planes.

With low magnification (Fig. 3) a considerable thickening of the epithelium by proliferation of the epithelial cells was observed. The tumour, 1 to 1·5 mm. in breadth, presented a flat surface; in one place, however, there was a clearly-defined extension formed by an epithelial proliferation into depth. In front of this formation conjunctival tissue was observed, in the midst of which could be seen a vessel penetrating between the epithelial cells close to the surface. This was one of the vessels in which the tumour follicles centred. The basal membrane everywhere was well preserved.

With high magnification (Fig. 4) one could see that the normal arrangement of the epithelial cells was disturbed. In some places, especially near the

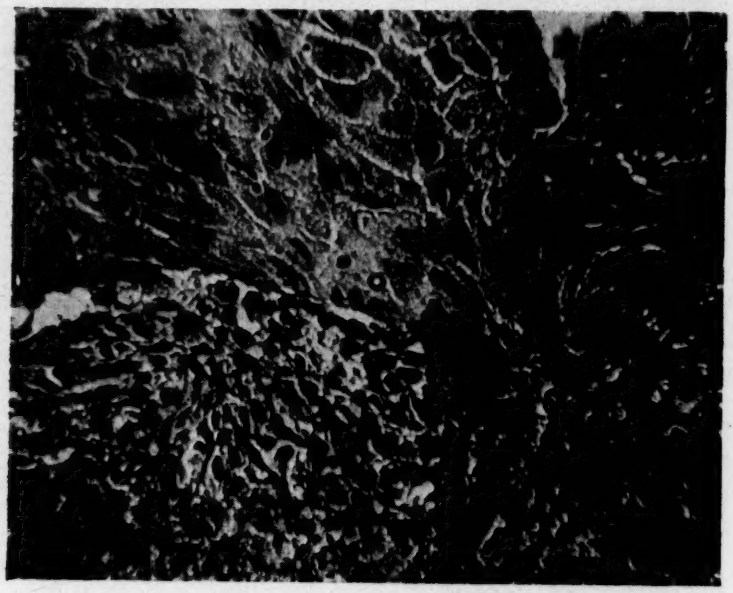

FIG. 4.—×800.

extension into depth, the cells were small and showed very chromatic nuclei. In other places, the cells were greater and presented pale and more or less irregular nuclei, containing one or two clearly-defined nucleoli. The binuclear cells were numerous. Here and there mitosis was to be seen. There was no keratinization nor epithelial pearls. Some polynuclears were to be found in between the epithelial cells.

This is a typical picture of intra-epithelial epithelioma (Bowen's disease). We did not, however, see any giant cells; this was also the case with Esterman, Laval, and Okrainetz.

The rather peculiar presence of an extension into depth indicated an increase in the malignity of the tumour, as it could be observed also in the tumour of Bowen (Khanolkar, 1946).

Therapy.—Our patient was submitted at once to contact radiotherapy in the service of Prof. De Backer: Philips Metalix tube; 50 kilovolts tension under 2 milliamp.; no filter; D.F.P. 40 mm.; surface of the localizator, lead; duration, 9 seconds; 51 r per session; sessions on May 23, 24, 25, 27, 28, 30, 31, and June 1, 3 and 7, 10 sessions in all; total 5·150 r.

Results.—On June 15 a very great improvement was noted (Fig. 5); the tumour had melted; the edge of the cornea was back to its normal gleaming aspect. There was no opacification outside the circular banal gerontoxon. On the level of the conjunctiva it was impossible to see any neo-formation; there remained only a scarcely perceptible thickening with rather pronounced local hyperaemia.

FIG 5.—June 15.

FIG. 6.—July 7.

FIG. 7.—July 27.

On July 7 there was no trace of humour left and the hyperaemia had considerably diminished (Fig. 6).

On July 27 recovery was complete, with no sequela whatsoever (Fig. 7). The eye is white and it is impossible to tell that it has ever shown any lesion. It has responded splendidly to contact therapy, no trace of which is left, not even the slightest symptom of irritation. Visual acuity is still 10/10. All refractive areas and the crystalline lens in particular remain absolutely transparent and there is no lesion of the inside of the eye.

Up to the present (*i.e.*, after 6 months), recovery remains total without any sign of relapse.

Our observation of intra-epithelial epithelioma of Bowen is interesting for three reasons:

(1) Though one comes across Bowen's disease fairly often on the level of the skin, it is very seldom to be observed on the level of the bulbar conjunctiva. Ours is the ninth case published.

(2) Contact therapy brought about a rapid and complete recovery, which is the second one obtained by this method, the first being that related by Esterman, Laval, and Okrainetz. These authors used a Chaoul tube; 60 kilovolts tension under 5 milliamp.; no filter; D.F.P. 10 cm.; 610 r a minute; duration 1·5 minutes; one session every two days; nine sessions, total 5·400 r.

(3) The eye has undergone contact therapy without the slightest damage. This is not so when one resorts to the usual radiotherapy, which inflicts ocular irritation and often opacifies the crystalline lens.

Therefore we advise contact radiotherapy in every case of intra-epithelial or even basocellular epithelioma of the bulbar conjunctiva.

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PRE-PAPILLARY CYST DEVELOPED FROM REMNANTS OF THE HYALOID ARTERY*

BY

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THE duct of Cloquet is a tubular area which traverses the eyeball in its anterior-posterior axis from the optic disk to the posterior pole of the lens. It develops at the expense of the central or original vitreous, which is progressively absorbed from the third month of intra-uterine life, during the formation of the definitive vitreous.

In the human foetus the duct of Cloquet exists from the sixth month and generally disappears shortly after birth. It contains the hyaloid artery, the ramifications of which form a vascular sheath embracing the posterior lens capsule. In young children, and even in adults, remnants either of the duct of Cloquet or of the hyaloid artery can sometimes be seen.

The duct of Cloquet may persist in the shape of a membrane, which is inserted into some part of the optic disk, covers the emergence of the vessels and ends in the vitreous, either in the form of a point or club, or in the form of membranous expansions. Some types of hyaloid remnants are easily recognized. The following are some examples:

(1) A white tubercle, bright and quite small found on the emergence of the central retinal artery like a bud on the bough of a fruit-tree.

(2) An arterial handle leaving the optic disk and projecting into the vitreous.

(3) A mobile cord or dark filament, arising from the optic disk and ending by a free extremity in the vitreous.

These prepapillary formations should not be mistaken for hyaline drusen at the optic disk or for the epipapillary membrane. The latter covers the whole of the optic disk and is attached to the vessels where they emerge. It may be opaque or transparent and somewhat ill-defined, and may encroach slightly upon the neighbouring retina.

Very exceptionally one can find prepapillary cystic formations, probably related to remnants of the hyaloid artery. The cases of Durst (1909), Risley (1896), Koller (1900), Paton (1910), Levitt and Lloyd (1939), Yudkin (1926), Hilgartner (1940), Levine (1932), Purtscher (1936) and Mérigot de Treigny and Subileau (1927) are

* Received for publication August 2, 1949.

well known. These cysts develop before or shortly after birth. They may resemble a tumour in size. Rounded and greyish, they are situated on the optic disk and project into the vitreous. They may have a stalk of variable length. The presence of blood has been detected and occasionally they have been mistaken for cysticercus cysts (Liebreich, 1854; Vassaux, 1883).

They develop from the vascular system proper of the hyaloid artery or from the glial tissue which surrounds it, or from the mesodermal tissue which penetrates the vitreous together with the artery, or from the potential space between the artery and its glial mantle.

According to Durst, the following characteristics distinguish a prepapillary or congenital papillary cyst from an acquired one:

(1) The existence of associated congenital anomalies.

(2) The absence of signs of old or recent inflammation.

(3) The absence of vessels.

(4) The presence of amblyopia and squint.

Case Reports

The following descriptions of prepapillary cysts, taken from the literature, are of interest.

1. *Levitt and Lloyd (1939).*—A well-defined and rounded cyst-formation, 3 D.D. in diameter and greyish-white in colour, covers part of the optic disk and of the neighbouring retina. In its lower half the retinal vessels run distinctly on the surface, whilst in the upper half, they are veiled, being situated behind the cyst. There are no pigment flecks, no exudates, no haemorrhages. Vision and visual field are normal.

2. *Yudkin (1926).*—At the upper nasal part of the optic disk, a whitish rounded mass, 2 dioptres in height and 1½ D.D. in breadth. This well defined but lightly pigmented mass is crossed by a fairly important vessel and a few other tiny vessels can be observed.

3. *Hilgartner (1940).*—In a 12-year-old child, on the level of the optic disk, there is a white, avascular mass, 5 dioptres in height and ½ D.D. in breadth. After a lapse of 5 years no change occurred in this mass. V.A. less than 1/10.

4. *Levine (1932).*—In a 14-year-old girl, a cystic avascular mass situated on the nasal margin of the optic disk, 5 dioptres in height.

5. *Risley (1896).*—The upper half of the optic disk is covered by a grey cystic tumour, transparent, avascular and 2 mm. in height. Under this tumour there is a hyaloid remnant, but there is apparently no anatomical relation between the two formations.

6. *Durst (1909).*—Astride the temporal margin of the optic disk is a cyst, rounded and grey and formed by a transparent and thin tissue. At the summit of the tumour, which is surrounded by a dim and dusty area of the vitreous, a few thin vessels are seen.

7. *Purtscher (1936).*—On the level of the upper-temporal quadrant of the optic disk, there is a rounded tumour, greyish-red in colour and 1 mm. in height. On its surface is a network of capillaries, some of which penetrate the mass. Simultaneously with the veinous retinal pulse, the tumour turns alternately red and pink, and when the eyeball is compressed it becomes quite pale and can be distinguished from the optic disc with difficulty.

8. *Mérigot de Treigny and Subileau (1927).*—The temporal half of the optic disk is hidden behind a bright whitish formation, of conical shape and irregular base. Being 3 DD. in breadth, it encroaches upon the neighbouring retina. Homogeneous and avascular, it has frayed edges. The eye is convergent, hypermetropic by 6 dioptres and amblyopic.

Personal Observation

A girl, aged two and a half years, brought to me on October 28, 1943, had developed, some months previously, a right convergent concomitant squint associated with bilateral hypermetropia. (R.E. : + 3·50 D., L.E. : + 2·50 D.)

Right eye.—Excluding the squint, no other lesion was apparent except a small whitish and fibrous streak, situated at the posterior pole of the lens. Visual acuity was less than 1/10 (amblyopia ex anopsia).

Left eye.—(See Figure). In front of the optic disk there was a voluminous bilobular cyst, 3 D.D. × 2 D.D., greyish in colour,

FIGURE.—Prepapillary cyst in left eye..

but transparent. Adherent to the disk and about 3 mm. in height, the cyst was slightly mobile. Two vascular bundles emerged seemingly from the posterior face above and beneath it and joined each other on the anterior surface of the cyst with the production of two unequal lobes. On the lateral temporal face of the upper-anterior lobe a small, rather short, vascular bundle was observed. On the nasal side of the optic disk there was a flat triangular formation, fibrous in appearance and rather vascular. There was no other ocular anomaly to report except for a remnant of the hyaloid artery at the posterior pole of the lens.

During the past six years the cyst has undergone no change either in structure or in volume. It can therefore be considered as congenital. The prepapillary situation and the integrity of the visual functions suggest that the optic fibres were not involved and that it was developed from remnants of the hyaloid artery.

In January, 1946, I observed below and within the macular region a few small punctiform haemorrhages (three or four). In October, 1947, these haemorrhages had increased in number, but in November, 1948, they had completely disappeared. In February, 1949, there was a new haemorrhage, at exactly the same site. (See Figure). I think I can ascribe these retinal haemorrhages to a mechanical irritation, brought about by the movements and the friction of the cyst.

It should be noticed that the visual acuity of the left eye stayed at 10/10 throughout and that it was the right eye which was convergent and amblyopic, although anatomically the better fashioned. This shows that the criteria of Durst for the differentiation of acquired and congenital prepapillary cysts do not always hold.

Finally it should be noticed that but for the ocular anomalies the child was normal and there was nothing relevant to report concerning her personal or family history.

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XANTHOMA CORNEAE AS HEREDITARY DYSTROPHY*

BY

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A PATIENT presented herself in 1944 at the Kivelä Hospital Polyclinic for Eye Diseases with central opacities of both corneae formed by small crystals. This finding led to the discovery of the cases described in this paper, and, although continuous observation has been possible in one case only, they are probably of sufficient interest to merit publication.

Case Reports

Case 1. K. A., the wife of an artisan, born October 13, 1909. Her father died of pulmonary tuberculosis at the age of 46, her mother at an advanced age

FIG. 1.—Case 1. Right eye.

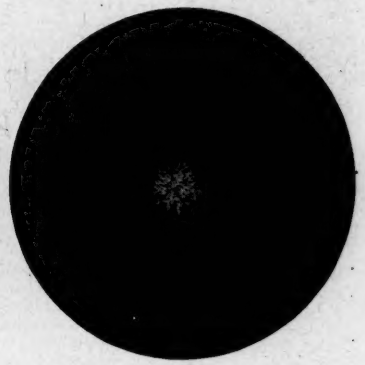

FIG. 2.—Case 1. Left eye.

of some unknown disease. According to the history, her parents and grandparents had normal eyes and good vision. The patient herself had always been healthy. She had been married 10 years, had no children, and no miscarriages. Menses regular, rather scanty. The patient's eyes had always been healthy. As a child she had noticed on both corneae small spots which had not changed in any way. Her vision had always been good.

Medical examination at the Department for Internal Diseases revealed nothing abnormal. Blood picture normal; blood uric acid 3·9 mg. per cent.; blood cholesterol 437 mg. per cent. *X*-ray examination showed no signs of gout. Hypoplasia uteri was noted in the gynaecological examination carried out at the Women's Clinic of Helsinki University.

Ophthalmological examination: R.V.=6/7·5, L.V.=6/5. The eyes were free from congestion. In the centre of both corneae were yellowish patches 2·5 mm. in diameter in the right eye, and 2×1 mm. in the left. At the edge of the

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cornea, about 1 mm. from the limbus was an opaque ring, 2 mm. broad, dense in the periphery and becoming less so towards the centre of the cornea. The slit-lamp showed that the yellowish patches consisted of glittering needle-like crystals situated just under the corneal epithelium and extending to the inner third of the cornea. The opacity at the edge was a structureless mass with no discoverable crystals. No blood vessels or vascular remnants were seen. The inner eye was normal on both sides.

The patient was seen periodically to date. She was given folliculin orally and dionin locally for 8 months, when this treatment was discontinued because the condition seemed to remain unchanged. The patient presented herself approximately every second month, and in the Autumn of 1947 the central opacity was found to be markedly smaller in both corneae; in the left it seemed to have very nearly disappeared and only a small number of isolated crystals could be seen by the slit lamp. The blood cholesterol was 243 mg. per cent. The patient said that in the preceding summer she had changed her diet and had

FIG. 3.—Case 2. Right eye.

FIG. 4 —Case 2. Left eye.

taken fat only in the form of butter. Otherwise she had lived mainly on vegetables. Her food had thus been poor in cholesterol.

After this the patient's condition changed comparatively little until early summer, 1948, when the opaque patches began to enlarge and the crystals in them increase. In the right cornea the crystals in the centre coalesced into a diffuse mass forming an irregular plate with holes. Crystals were also seen in the periphery. The blood cholesterol had again increased and was now 328 mg. per cent. In spite of the enlarging opaque patches and their increasing density the patient's vision deteriorated very slightly. She had gradually returned to her former liberal diet, because she found the restricted diet too expensive.

Case 2. P. A., brother of Case 1, born March 3, 1897. He had had various infectious diseases, and had been suffering from dyspepsia for a considerable time. His eyes had always been healthy, but of late he had noticed some dimness when reading. He did not admit to having noted anything abnormal in his corneae.

Medical examination at the Department for Internal Diseases at the Kivelä Hospital revealed achylia gastrica; pulmonary emphysema; normal renal function. Blood picture normal; blood calcium 11·3 per cent.; blood uric acid 4·0 mg. per cent.; blood cholesterol 274 mg. per cent.

Ophthalmological examination: R.V.=6/7·5 c+2·0 D.S. L.V.=6/10 c+1·5 D.cyl. axis 150°. Both eyes were quiet and free from congestion. In the centre of both corneae opaque patches about 3×4 mm. in extent. Ring-like opaque patches at the margins of the corneae, resembling those noted in the former patient. When examined by the slit-lamp the marginal opacity was found to be diffuse.

The central opaque patches were diffuse in the middle, greyish-yellow in colour, and occupied two-thirds of the thickness of the cornea. In the upper and lower margins of this diffuse centre, vertical, glittering, yellowish, needle-shaped crystals were seen superficially as in Case 1. No open or obliterated blood vessels were present. The deeper parts of the eyes were normal.

Case 3. P. K., brother of Cases 1 and 2, artisan, born January 6, 1914. He had been treated for nephritis several times and had once suffered from polyarthritis. He had also been hospitalized for gastric ulcer. At 13-14 years the patient had noticed that there was something the matter with his eyes but could not remember what. There had been no subjective symptoms in the eyes and he had always seen well.

Medical examination at the Department for Internal Diseases revealed duodenal ulcer and chronic nephritis. Blood picture normal; blood uric acid 3·5 mg. per cent.; blood cholesterol 257 mg. per cent.

Ophthalmological examination: R. and L.V.=6/5. The eyes were quiet, no congestion. In the centre of both corneae semi-circular opaque patches with a

FIG. 5.—Case 3. Right eye.

FIG. 6.—Case 3.—Left eye.

radius of 3 mm., the thickness of the arc being 1·5 - 2 mm. The arcs were open temporally. In the marginal parts of the corneae there were opacities similar to those noted in cases 1 and 2. The central opaque patches were of crystals similar to those in the cases described above and the crystals were present in the same corneal layers. In this case it could be seen very clearly that the crystals had settled mainly in radial formation. No coalescence was noted. The deeper parts of the eyes were normal.

One week after the examination at the hospital the patient developed anuria at home and was re-admitted to the Department for Internal Diseases. His condition became rapidly worse, but he himself and his relatives wanted him discharged from hospital. He died after a couple of days. Permission for autopsy was withheld.

Case 4. Son of Case 3, born August 15, 1941. When three weeks old the patient had been treated at the Children's Department of Maria Hospital for some eruption of the skin. Opacities in the corneae had been noted at that time, but he had never been examined by an eye specialist. The patient had been otherwise healthy.

Medical examination at the Kivela Hospital Department for Internal Diseases: general health good, nothing pathological noted. Blood picture normal; blood uric acid 4 mg. per cent.; blood cholesterol 285 mg. per cent.

Ophthalmological examination: R. and L.V.=6/4. The eyes were quiet, uncongested. Elliptical opaque patches were noted in the centre of the corneae, the clear centres of the opaque patches were 2×3 mm., the thickness of the arc

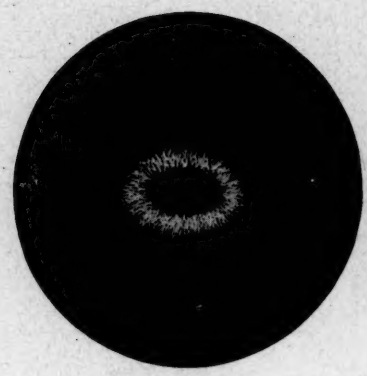

FIG. 7.—Case 4. Right eye.

FIG. 8.—Case 4. Left eye.

about 2 mm. Examination by the slit lamp showed the opacity to be formed of similar crystals in the same junction as in the former cases. No coalescense was noted. In the marginal parts of the corneae the opaque rings were rather indistinct. The deeper parts of the eyes were normal.

Discussion

We have thus three siblings and the child of one with similar changes in the corneae. Although only two generations were observed, we are obviously dealing with a hereditary phenomenon. The disease is characterized by slow development, lack of irritation and lack of corneal blood vessels, and according to the histories begins in early childhood. Although we have been able to follow only one patient to date, yet a composite picture of the disease and its course can be built from the symptoms and signs in this and the other cases.

Although the disease is hereditary, other factors contribute to its development. Diet evidently plays an important role in the genesis of the disease. These patients showed a marked tendency to increased blood cholesterol, which in one case was controlled by restricted intake.

By giving cholesterol to laboratory animals, this substance appears even in a healthy cornea and artificial gerontoxon is produced. The condition, in fact, seems to be an intermediary between the physiological corneal changes of old age and the pathological changes of dysthropy. Kohashi (1929) fed animals on lanolin and produced an opacity in the centre of the cornea, and further found that the severing of the seminal duct caused clearing of the corneal opacities in some cases, although the lanolin diet was continued without interruption. This proves that an excess of

cholesterol is not the only factor causing storage of the substance in the cornea.

Looking for similar cases in the literature, we first examined the descriptions of hereditary corneal dystrophies given in most textbooks classified after Bücklers (1938). Our cases, however, do not fit into these groups, although they undoubtedly belong to the hereditary primary corneal dystrophies. Axenfeld (1930) defines the condition as a change in the transparency of the cornea, not due to any external cause such as injury, infection, inflammation, or physical or chemical effect.

We also found in the literature a few cases of hereditary crystalline degeneration of the cornea, first described by Schnyder (1939). Both Cavara (1940) and Pandolfi (1941) published similar reports. Their descriptions of the disease and the pictures published correspond exactly with our cases in regard to both the hereditary character and the ophthamological picture.

Schnyder did not give the blood cholesterol values of his patients, but in Cavara's and Pandolfi's cases these were within normal limits, while in each of our own cases the blood showed an evident increase of cholesterol.

In the literature there are no cases of hereditary corneal dystrophy with elevated blood cholesterol. Among the non-hereditary corneal dystrophias, on the other hand, corneal xanthoma with lipid changes is mentioned. This disease and our cases are both characterized by lack of irritation, the presence of crystals, and a diffuse opacity in the cornea, with increase in the blood cholesterol.

The fact that Axenfeld noted clearing of the opacity in one case of xanthoma corneae is a very important feature. Zeeman and Groen (1947) succeeded in producing complete clearing of the cornea with a strictly vegetarian diet. Their treatment was based on Schoenheimer's statement that man is unable to absorb sterols from vegetables. This is in agreement with the corneal clearing and decrease of crystals noted in our first case as a result of the patient's adopting a vegetarian diet of her own accord.

These facts suggest that in our cases the opaque patches were due to cholesterol crystals. It is true that crystals were of unusual shape, but Schoenheimer (1923) has shown that the cornea is the only place where cholesterol crystals are found, *intra vitam*. in the form of anisotropic needles.

Axenfeld assumed that in cases of xanthoma the cornea is capable of only partial consumption of certain substances, which are therefore stored. Animal tests, on the other hand, show that a healthy cornea has the capacity of storing cholesterol when there is a surplus. In our first case the blood cholesterol, still considerably above normal, had in fact decreased though when the conspicuous reduction in the amount of the corneal crystals was noted.

As our cases are similar to those of Schnyder (1939), Cavara (1940), and Pandolfi (1941) in hereditary character and ophthalmological picture, we assume that they are examples of the same dystrophy. In Cavara's and Pandolfi's cases the blood cholesterol was normal, but we may suppose that in their cases the incapacity of tissues to make use of cholesterol was so marked that storage took place even when the cholesterol value was normal.

On the other hand, our cases seem to have features in common with xanthoma corneae, including the increase in blood cholesterol, and the varying of corneal opacity with changes in the blood cholesterol content. These cases may be regarded as an intermediate form between corneal xanthoma and hereditary crystalline dystrophy of the cornea. In any case they are a hereditary form of corneal xanthoma.

Summary

One sister, two brothers, and a child had in the middle of their corneae opacities formed by needle-like crystals, and in the marginal parts ring-like opacities resembling gerontoxon. They all showed an increase of blood cholesterol. In one case the cholesterol content of the blood fell when the patient adopted a strict vegetarian diet, and at the same time the number of the corneal crystals was reduced and the opacity cleared. The crystals in the cornea increased along with an increase of the blood cholesterol. None of the patients had any symptoms of irritation. We are probably dealing with a hereditary form of xanthoma corneae, which connects this disease with hereditary crystalline dystrophy of the cornea as described by Schnyder, Cavara, and Pandolfi.

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HYALURONIDASE AS A SPREADING FACTOR IN THE CORNEA*

BY

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THE permeability of the connective tissue throughout the body is controlled by the state of the interfibrillar ground substance. This ground substance has several components in nature, some protein, some mucopolysaccharide; the latter are the important factors in controlling the permeability of the tissue since, being highly polymerized, they form a viscous barrier to the diffusion of particles of colloidal dimensions. Skin contains two mucopolysaccharides, hyaluronic acid and chondroitin sulphate, in the ground substance of the dermis, while the cornea is stated to contain hyalurono-sulphate. Hyaluronic acid and hyalurono-sulphate can be broken down (depolymerized) by an enzyme hyaluronidase found in the filtrates of certain bacteria and in extracts of testis. The enzyme preparations of testis have also the power of depolymerizing chondroitin sulphate. Intradermal injections of hyaluronidase facilitate the diffusion of dyes, viruses, or toxins, by breaking down the viscous barrier offered by hyaluronic acid and this effect is the basis of the " spreading reaction ".

The mucopolysaccharide of ox cornea was characterized by Meyer and Chaffee (1940) as hyalurono-sulphate (a sulphate ester of hyaluronic acid) on the basis of its composition and because it was hydrolysed by hyaluronidase preparations from filtrates of the pneumococcus and testis. They suggested that the normal transparency of the cornea and its lack of blood vessels depended on the presence of hyalurono-sulphate and showed that these characteristics were abolished by injections of hyaluronidase.

Wislocki, Bunting, and Dempsey (1947) found that the metachromatic staining reaction of cornea with toluidene blue was not abolished by treatment with testicular hyaluronidase, but drew no conclusions from this observation. It is possible that a small decrease in the intensity of staining would pass unnoticed under the conditions used by these authors. A further investigation of the nature of the mucopolysaccharides of the cornea was clearly required, and it was decided as a first step to assess the activity of hyaluronidase as a spreading factor in this tissue. Meyer had obtained a positive reaction using pneumococcal and testis enzymes.

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It may be stated that a positive spreading reaction in a tissue using hyaluronidase provides strong evidence for the presence of the substrate (hyaluronic acid or hyalurono-sulphate) in that tissue, but this is not conclusive since no hyaluronidase preparations have been completely purified. A negative spreading reaction with a hyaluronidase preparation provides evidence for the absence of the substrate in that tissue provided that the conditions for the spreading reaction hold—that the mucopolysaccharide alone acts as a barrier to diffusion.

The subject is also of importance since clinical uses of the spreading reaction have recently been suggested (Gaisford and Evans, 1949; Atkinson, 1949), and hence a knowledge of the activity of hyaluronidase as a spreading factor in the cornea is of value apart from the evidence it provides of the nature of the mucopolysaccharides.

Methods

Testicular Hyaluronidase was prepared from bovine testis according to the methods of Madinaveitia (1941). In one case an acetone powder was prepared from the aqueous extract of testis, in the other the aqueous extract was treated directly. The solution resulting from fractionation was dialysed against 0·9 per cent. aqueous NaCl.

Cl. Welchii Hyaluronidase was prepared according to the directions given for "crude hyaluronidase" by Rogers (1946). Hyaluronic acid from ox vitreous body was added to the growth medium.

Streptococcal Hyaluronidase was prepared according to the method of Rogers (1946) for "crude hyaluronidase". The filtrate was from a culture of a strain of streptococcus haemolyticus group A.

Pneumococcal Hyaluronidase. A type III pneumococcus was grown in a serum broth containing hyaluronic acid. The filtrate was not fractionated.

Haemoglobin Solution. Rabbit blood corpuscles were washed six times with 1 per cent. NaCl, laked with distilled water, and centrifuged, and the supernatant was dialysed against 0·9 per cent. NaCl.

Hyaluronidase Activity was always determined on the mixture of enzymes and indicator, by means of the spreading reaction in guinea-pig skin and the polysaccharide disaggregation test prescribed by Pirie (1949). At first it was hoped to use Evans blue 1 per cent. in 0·9 per cent. NaCl. as indicator, but this was found to inhibit hyaluronidase action in the polysaccharides disaggregation test. Thus a testis enzyme plus Evans blue solution (1 : 1v/v) took 94 mins. for the mucopolysaccharide to be disaggregated, whilst the testis enzyme plus 0·9 per cent. NaCl. (1 : 1v/v) required less than 60 seconds.

Collagenase from Cl. Welchii was a gift from Dr. E. Bidwell of the Welcome Research laboratories. As provided, the enzyme had an activity of 18 Q/ml.

Nitrogen was measured by the micro-kjeldahl method.

Spreading Reactions. These were of two types:

(*a*) Rabbits were anaesthetized with nembutal and the enzyme + indicator solution injected into the stroma of the cornea of one eye, and the control (boiled enzyme + indicator) into the other eye. The blebs were measured after injection, and after the time interval allowed for reaction, and finally (after killing the animal) the latter measurement was confirmed on the excised cornea. With careful injections of 0·05 ml. a circular bleb of initial mean diameter 4 to 6 mm. was consistently produced.

(*b*) Isolated ox cornea were placed on squared graph paper covered with filter paper pads soaked in 0·9 per cent. NaCl, and kept at 37°C. The mean initial diameter of the bleb was 8 to 10 mm.

As had been anticipated from the compact structure of the cornea, diffusion was very slow. Accordingly it was decided, in the later experiments, to depart from the conventional pattern of spreading reactions (Bacharach and others, 1940; Humphrey, 1943), and to wait long enough for a significant increase in diameter in the control to have taken place. Measurement was to 0·5 mm., so the significant increase in diameter demanded was 10 per cent. in rabbits and 5 per cent. in ox corneae.

Results

The activity of the mixture of enzyme and indicator was such that in all cases the time required in the disaggregation tests was less than 60 secs. All enzymes gave a positive spreading reaction in guinea-pig skin. The results set out in Table I and II indicate

TABLE I

Rabbit Corneae

Source of enzyme	No. of animals	Mean % increase in diameter		Time allowed (mins.)
		enzyme	control	
Testis ...	4	0	0	30
	1	0	0	81
	3	14	10	144
Cl. Welchii	2	12	12	160
Pneumococcus	3	14	12	180

TABLE II

Ox Corneae

Source of enzyme	No. of corneae	Mean % increase in diameter		Time allowed (mins.)
		enzyme	control	
Testis ...	5	8	7	130
	4	58	64	1,275
Cl. Welchii	4	52	52	1,275
Streptococcus	3	22	20	360

Diffusion from the bleb produced by injections into the stroma of cornea. Controls contained heat-inactivated enzyme.

no significant difference in the diffusion from the blebs containing enzyme from those acting as controls.

It was considered that if the spreading action of hyaluronidase were very slight it might reveal itself if the compact collagen fibre network could be modified to facilitate diffusion. To that end, two experiments were performed, one involving a swelling of the interfibrillar material (Day, 1949), the other destruction of the collagen fibres.

(*a*) Ox corneae were placed in distilled water for 2 to 3 hours. They became swollen. After injection in the standard manner the mean diameter with both enzyme and control increased by 18 to 20 per cent. in one hour.

(*b*) The collagenase solution was found to be active in corneal collagen by a modification of the test described by Bidwell and Van Heyningen (1948) under "Estimation of digestion of hide powder". A 60-mesh powder of ox cornea which had been extracted with water and acetone was used as substrate. 400 mg. of this powder were incubated at 37°C., with 10 ml. Palitzsch borate buffer *p*H 7·09, and 1 ml. collagenase (18 Q/ml.). The control contained heat-inactivated enzyme. After two hours the filtrate from the solution containing the enzyme had 110 per cent. more total nitrogen than had the control solution. The following solutions were made up:

Collagenase + streptococcal hyaluronidase + Hb (1:1:1).
Collagenase + boiled „ „ + Hb (1:1:1).

Injection into a living rabbit cornea gave a 20 per cent. increase in the mean diameter of the bleb in two hours with each mixture. Comparison of the degree of spreading in both water-swollen and collagenase-treated corneae with that in the untreated cornea indicates a significant increase in the rate of diffusion. Yet even under these conditions hyaluronidase exerted no action as a spreading factor.

Discussion

It is considered from these experiments that hyaluronidase has no action on the corneal mucopolysaccharides, *in situ*, at least within 24 hours. Accordingly, the suggestion of Mayer and Chaffee (1940) that the observed corneal vascularization following the injection of hyaluronidase was due to the breakdown of the mucopolysaccharides deserves reconsideration.

It is considered that the evidence from spreading reactions alone is insufficient to allow the conclusion that the substrate for hyaluronidase is absent from the cornea. Work is in progress on the fractionation of the mucopolysaccharides of ox cornea. A solution of a material prepared by $CaCl_2$ extraction, which, from its analytical figures, could be a mixture of 60 per cent. sulphated mucopolysaccharide and 40 per cent. protein, gave a relative viscosity in buffered saline of 1·6 for a concentration of 0·3 per cent. This viscosity was not reduced by hyaluronidase action, nor did

the solution acquire reducing properties. Full details of these experiments and of the extractions will be given in a further paper.

The presence in pneumoccccal filtrates (used by Meyer as a source of hyaluronidase) of other enzymes which attack structures in the cornea would provide a possible explanation of the positive spreading reaction he reports. Presumably the spread of the ulcer produced by pneumococcal infection is effected by enzymatic processes. However, the positive spreading reaction reported to be found with testis enzyme would be difficult to understand.

Summary

(1) Hyaluronidase from several sources has been found to be inactive as a spreading factor in rabbit and ox cornea.

(2) The suggested action of hyaluronidase in causing vascularization in the cornea by breakdown of the mucopolysaccharides is discussed.

Acknowledgments

The author wishes to express his gratitude to Dr. H. Davson for his interest and advice in the course of the work and in the preparation of the paper; also to Dr. N. Crowley for a strain of streptococcus and to Dr. E. Bidwell for the collagenase preparation.

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CHANGES IN THE FUNDUS CAUSED BY POLYCYTHAEMIA*

BY

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THE aetiology of polycythaemia vera is unknown. This disease mainly consists in a remarkable increase in the red blood corpuscles and in the entire quantity of the blood. It is more frequent in men, mostly between the ages of 40 and 50. Generally there is hyperaemia of the face, the conjunctiva, and the fundus. The presence of a spleen tumour is important. The changes in the fundus are more or less those called cyanosis retinae by Liebreich, and when we speak of fundus polycythaemicus this is in our mind, although Liebreich described these changes in connection with morbus coeruleus. The colour of the fundus is darker red, the veins are greatly enlarged and tortuous. Very many veins are visible because even the smallest veins are filled with blood.

Besides all these changes, papilloedema was described by Behr and Hegner, haemorrhages of the retina and of the vitreous by Litauer and Januszeveski (1934), and newly-formed vessels by Ohashi and Okada (1939). Uhthoff (1906) observed characteristic dilatations of the larger veins, and Behr dilatations of the capillaries, which according to them do not occur with other diseases.

The above-mentioned changes do not, however, explain the temporary deterioration of vision of which most patients suffering from polycythaemia complain. Generally it lasts for a few minutes, mostly on one side. Raynaud pointed out that spasm of the central retinal artery might account for cases of temporary sudden loss of sight. In two cases of polycythaemia Elschnig and Nonnenbruch (1932) found unilateral embolism of the central retinal artery and believed a spasm to have caused it. Köster (1906) found transitory reduction of the field of vision in patients suffering from polycythaemia and supposed it to have originated in a spasm of the cerebral artery. Ultimately Mylius (1928) was the first to observe a transitory spasm of all the branches of the central retinal artery in one eye of a patient suffering from polycythaemia. Later Lisch (1940) reported a similar case with temporary spasm of the central retinal artery. Thus, all in all,

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two cases are known in which it was possible to observe the supposed artery spasms and to photograph them.

This communication contains observations of changes of the fundus in thirteen cases of polycythaemia. With new data it aims at confirming the observations and suppositions of Mylius (1928) and Lisch (1940), *i.e.*, that the role of the arteries is not unimportant in the picture of the fundus in polycythaemia. Some of the patients were observed for several months and many examinations were necessary in order to identify different signs.

Details of Two Cases

Case 1.—Male patient, 24 years old, suffering from polycythaemia for one year. A few months previously his left arm and left leg became paralysed for several weeks; later the paralysis subsided. For the last two weeks he had temporarily

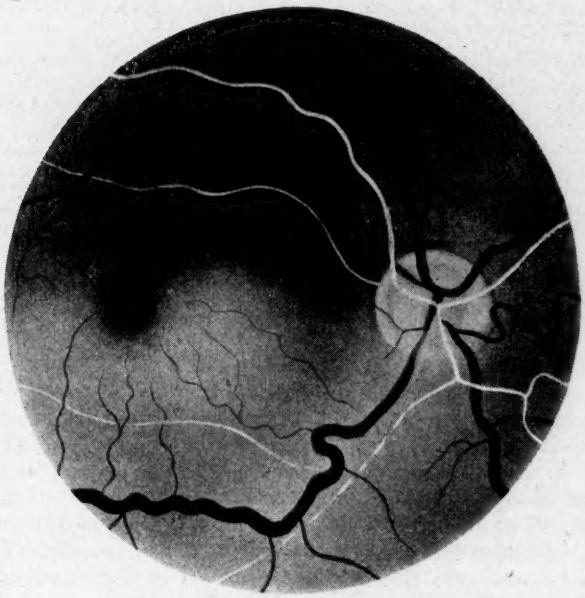

FIG. 1.—Case 1, male patient, 24 years old, right eye.

lost the sight of the right eye completely for a few minutes. During the last four days, however, amidst similar symptoms, vision in the right eye had suddenly deteriorated and not returned.

The medical report was as follows: Red blood corpuscles count, 8·8 million; blood-pressure, 150/120; tumour of the spleen; liver swelling.

The ophthalmological report was as follows: Visual acuity in the right eye, finger count at 1/2 m.; left eye 5/5; fundus in right eye; lower nasal border of the optic nerve blurred. The central retinal artery under the temporal branch near the disk was highly narrowed, the blood column inside was interrupted in several places. Alongside the vein the retina was oedematous and greyish-white, the oedema extending as far as the lower half of the macula, the fovea brighter red. The veins were dilatated to three times their normal size in places, especially the lower temporal vein. On the periphery in the direction of 2 o'clock a few thin, white, thread-like, empty arteries and small punctate haemorrhages. The left eye showed no visible changes except considerable dilatation of the veins.

During one of the examinations all the arteries of the right fundus suddenly turned into white, thread-like structures, while the small arteries disappeared, the blood column being completely expressed from them. This could be observed and photographed twice. Fig. 1 shows a drawing of a photograph of the fundus. On both occasions the lumen of the arteries gradually reopened in 10-15 minutes. During the phenomenon the patient had felt nothing at all, and the oedema remained unchanged. Visual acuity deteriorated during the spasm to seeing movements of the hand. About two weeks later, after different vasodilators and spasmolytics had been administered, the spasm of the lower temporal artery was relieved, the oedema disappeared, and visual acuity improved to 5/20, the field of vision being greatly reduced.

Case 2.—Female patient, 40 years old, under treatment for five years.

The medical report was as follows: Red blood corpuscles count, 6·5-7·5 million; blood pressure, 170/120; large tumour of the spleen; liver swollen; myocardial lesion.

The ophthalmological report was as follows: Vision blurred from time to time, the right eye being sometimes absolutely sightless for 1-2 days. Once we succeeded in observing a spasm like that described in Case 1; it expanded to all the branches of the arteries and lasted for only a short time during which the arteries turned into white thread-like structures. The picture resembled that shown in Fig. 1 without the oedema. Visual acuity of the right eye deteriorated to finger count at 1 m. distance, but after the spasm had ended, sight was completely restored within a few minutes.

Discussion

The complete absence of blood in the arteries as shown in Fig. 1 is a change which can so rarely be observed that in other diseases (eclampsia, migraine, etc.) it has hardly ever been possible to find it so soon. After the spasm had ended, it was so evident that the arteries filled again from the direction of the disk that there could be no doubt as to their having been emptied by the spasm. Besides the cases of Mylius and Lisch, my Case 1 is—as far as I know—the third to be described in literature, and my Case 2 is the fourth in which a similar complete spasm could be observed.

Unlike the other cases, in my Case 2 broad white stripes could be seen alongside the walls of the arteries and veins, probably because of changes in the walls and their direct surroundings, which were certainly related to the lasting spastic state.

My third case is an example of the finding of Uhthoff, who believes that the partial dilatations of the veins are most characteristic. In Fig. 2 we can see such a partial ectasia in one of the nasal veins, which was all the more striking as it was a much darker red. Dilatations of the veins to so high a degree, and such distinct tortuousness of even the smallest veins, generally only occur after a long time and usually only when the heart is no

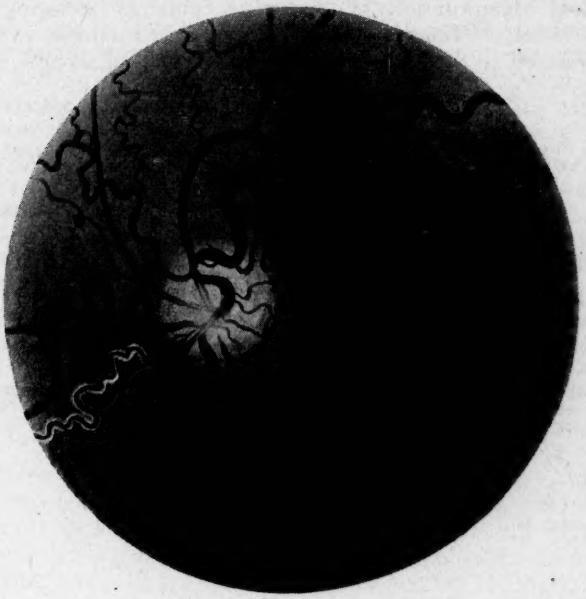

FIG. 2.—Case 3, example of partial dilatation of vein as described by Uhthoff.

longer strong. Papilloedema is also visible in Fig. 2, but this was much more developed in another case. Among my cases I also found an example of the formation of new blood vessels, and retinal haemorrhages.

In the other cases the pictures of the fundi were not different from the well known type of fundus polycythaemicus. In every case the darker red colour and the dilated veins could be observed, so that the fundus was characteristic of the disease in every case. In one case it was the examination of the fundus which suggested polycythaemia, and the medical report justified this suggestion.

Summary

When determining fundus polycythaemicus we must scrutinize the arteries as well as the veins. Among thirteen patients we observed important changes of the arteries in two and we succeeded in observing a spasm which spread to all the branches of the central retinal artery. On account of this case and two others, previously reported in the literature, we must consider spasm of the central retinal artery to be the cause of transitory deterioration of vision in patients suffering from polycythaemia. Temporary paralysis of the extremities must also be attributed to prolonged spasm of the cerebral vessels.

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THE PSYCHIATRIC ASPECT OF MINERS' NYSTAGMUS—II.*

BY

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IN a previous paper it was shown that miners' nystagmus is a disorder of emotional and not of organic origin. This research is part of a larger investigation, embracing various aspects of the disease and it was found that, in accordance with expectation in a psychogenic disorder, when objective methods only were used as in vitamin estimation in the blood (Campbell and Tonks, 1948), there was no significant difference between those affected by the disease and others, but that when subjective methods were used, a difference might be found, as in binocular vision (Campbell, Harrison, and Vertigen, 1948), or not, as in dark adaptation (Sharpley, 1948).

The emotional aetiology has received further confirmation from consideration of the geographical distribution. For perusal of the figures for miners' nystagmus in this country during the last few years when arrangements for compensation were stable, shows that they are capricious in distribution from pit to pit and from district to district, and inconstant in numbers from time to time. In the second report of the Medical Research Council (1923) it was found that in America where no compensation was paid there was virtually no complaint of miners' nystagmus, and that in Belgium where such compensation was not paid for more than six months, 98 per cent. of miners recovered within this period. In Germany, the cessation of payment of compensation for mild cases of miners' nystagmus was followed by a fall in the number of cases to one-tenth in five years, whereas in Great Britain the reverse process was followed by a rise in numbers. It is difficult to conceive of an organic disease which would behave in this way, but such behaviour is characteristic of emotional disorder.

Precipitating Causes

In my previous paper (Stern, 1948) the mechanism and predisposing causes of miners' nystagmus were elicited. A mental illness, however, has a precipitating as well as a predisposing cause and the investigation to determine the former is described below.

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Method.—The material consisted of 35 certified cases of miners' nystagmus, *i.e.* men who had already ceased work because of it, had been sent to Higham Grange Centre for rehabilitation, and were seen there between November, 1947, and July, 1948. A standard psychiatric examination was carried out in each case, as in the first portion of this research, and opportunity was taken to check the results with those then obtained. At the conclusion of this examination the man's confidence had been obtained and he was asked to what he attributed his breakdown. It was found that the answers were frank and ingenuous. Each case sheet was later perused and summarized and the most likely precipitating cause having regard to the total clinical state. The results were as follows:

(*a*) In eighteen cases, the breakdown was attributed to the man finding the work too hard or too harassing; three examples follow:

Case 1. A.H.D. (41).—A conscientious man with a good deal of insight, who is prone to anxiety. When asked the cause of his breakdown his reply was so cogent and fitted in so well with my own conclusions that I give it in full. "I think the nystagmus is caused because the miner has got too much to do in the time. If you go regularly and do not take time off it gets you in the end because of the strain." When I asked him if he found it harassing, he said, "Yes, it was too harassing for me. It's day after day and you are at full stretch. It is not the same at every pit; we chaps have taken on more than we ought for the nation's sake. There is no doubt it is telling on a good many more. It is all rush in the pits to-day."

Diagnosis: Hysteria.

Case 2. A.H. (50).—This patient is an insignificant person, very like Low's "little man." His main trouble is an intermittent hysterical tremor, which sometimes involves the left upper limb and at other times his whole frame. He says that it came on two years after an accident, apparently a minor one, to the right knee, and admits that he never liked mining and left the coal face because he found the work too hard. He still tends his garden and wishes to become a professional gardener. I can find no physical signs in the nervous system.

Diagnosis; Hysteria.

Case 3. W.F.R. (53).—A rather dull man, who attributes his trouble to overwork and electric lighting, but also says that his eyesight was failing. He has, in fact, refractive errors in the eyes, and it appears that this visual failure greatly worried him. "If I'd stopped underground longer I would have run into something and got killed. I am glad I finished, though I ought to have done so years ago."

Diagnosis: Fixation Hysteria.

(*b*) In eleven cases anxiety seemed to be the precipitating cause of breakdown, this anxiety having been converted into hysterical symptoms to a varying degree. It was usually an anxiety resulting from the hazards of work, and of this one is given, but in one illustration the anxiety case was due to a fault in marital life.

Case 4. J.B. (54).—An anxious man who has always feared pit accidents so much that at the outbreak of each war he enlisted at once, preferring the risks of battle to those of the mine. He appears to have been quite unnerved by an accident which he suffered 3½ years before his breakdown.

He states that his father after 21 years in the Marines worked down the pit for six months and then "found it a mug's game, so he went on the surface."

This patient himself has worked in eleven different collieries, transferring on one occasion because he narrowly missed an accident. He says, "My job was one of the most dangerous in the pits, drawing the wastes—you're drawing 'timber' to let the rest in. They were steel trees." When asked which he preferred, he said, "Well, I prefer drawing wood, but setting steel." He said, "I want a safe job, *e.g.*, in the lamp room cleaning lamps. With a dangerous job I feel all of a shake. I'm as if I was old before my time."

He is a rather dull subject who wears dark glasses and is suspicious.

Diagnosis: Hysteria, with some anxiety.

(*c*) In two men, breakdown resulted primarily from the disability caused by a major psychosis.

(*d*) In one case the cause appeared to be dissatisfaction with the work.

(*e*) In one case the cause was apparently domestic upset.

(*f*) In one case there was no disability from miners' nystagmus or other psychoneurosis, the certification resulting from a finding in detailed examination by the doctor treating the man for a limb injury.

(*g*) In one patient the aetiology was uncertain.

These results may be tabulated as follows.

TABLE

Cause of breakdown with miners' nystagmus	Number	Percentage
(*a*) Work, too much strain	18	51
(*b*) Anxiety	11	31
(*c*) Major psychosis	2	6
(*d*) Dissatisfaction with employment	1	3
(*e*) Domestic trouble	1	3
(*f*) Accidental finding (no real breakdown)...	1	3
(*g*) Doubtful—possibly high dark threshold	1	3
Total	35	100

Discussion

The commonest cause of breakdown, accounting for half the cases, is a feeling of inability to cope with the work. This occurs particularly when mental or physical powers are inadequate to the strain. It explains the shape of the histogram of ages at onset of miners' nystagmus given on p. 217 in my previous paper (Stern, 1948), in which there is a normal type of curve including the majority of cases, followed by another rise between the years 60 and 75, which appears to be caused by the waning powers of old age due to the onset of dementia or physical failure. A major psychosis with consequent dementia has a similar effect. Allied to inability to cope with the work is dissatisfaction with employment (*d*) which does not really merit a separate heading. Cases

2 and 3 were of mixed aetiology showing factors of those classed under (*b*) as well as (*a*).

In stating the reasons for breakdown, many of the miners showed good insight, particularly Case 1. How they may feel about their conditions of work has been well expressed by an intelligent ex-miner (Coombes, 1945). I quote his remarks although they refer more especially to pneumoconiosis:

> "In his mining work he was a craftsman . . . Yet, although not more than middle-aged, he was beginning to lose weight, and he was tiring more easily. The mountain was beginning to conquer him. I wondered if there was something about that realization which was influencing his desire for knowledge.
>
> "I have noticed it so often in the men who are beginning to age. They may have been twenty-five or thirty years underground, and if they had been in some jobs would have qualified for a pension. In the mines they feel their strength going and the limbs stiffening. The fear creeps into their consciences that their best days are gone; that even all their experience will not counterbalance their weakening body. They guess their wage packet will get steadily smaller, and they have no reserves put away. It is a grieving realization, and must cause a deal of the bitterness which sours mining life nowadays. No hope for the future, no security for the family. The only prospect, when he cannot answer the call for work, is the miner's pension—parish relief.
>
> "When their working days are past, what can the majority of them do? Most had no interest outside their work; when that fails them they are adrift from all their connections. They know not what to do with their hands or their minds. The pit wheels revolve, the dust cloud arises, the loaded trucks are taken away and they have had no share in its doing. Nor can they do any other work. I feel that every man should have some training in a second occupation that he could take to when his greatest strength fails. I know that few light jobs will ever be available at collieries, but would it not be possible to fit them for a factory job after, say, twenty years in a mine? That is a long enough slice from a man's lifetime to be spent away from the sun and daylight, in frequent danger and breathing forced air. Anyway, they should never be allowed to feel unwanted."
>
> "Nor does the urgent, rushing pace of mining work help much to accommodate a man to the more leisurely pace of surface work."

Many of the miners investigated here expressed similar feelings though they were less articulate. They feel that too much is expected of them in the pit — "Doth God exact day-labour, light deny'd?" they fondly ask.

That anxiety (*b*) is a precipitating cause of breakdown in one-third of the cases is not surprising in such a dangerous occupation, and there was clear evidence that in most cases this anxiety was related to the hazards of underground work. Its fixation on the eyes is to be expected, because they are the most important organs to the miner and his *locus minoris resistentiae*. This anxiety is converted into physical hysterical symptoms which have a symbolic meaning—the eyes, and sometimes other parts, tremble with fright, the blepharospasm and blinking show fear of injury and are also related to the need for frequent blinking in a dusty atmosphere (Lawson, 1948). The photophobia shows failure to

adapt to changing conditions of illumination, and the headache and giddiness symbolize worry and bewilderment.

The other precipitating causes are of little importance, but a case shows how unwise it is to communicate an incidental finding to the patient.

The peculiar character of the miner merits consideration. He is naturally a little suspicious, and although the men were sent to a rehabilitation unit it was felt that individual psychotherapy would be difficult and of doubtful value. It was found that their mere coming to the unit caused some emotional trauma, for many had never been away from home in their lives, and one left after only one day, stating that he was too homesick to remain. Miners generally are childish and dependent, and of the total of 85 married miners interviewed in the course of this investigation, excluding widowers and those married more than once, 26 (31 per cent.) had wives older than themselves, suggesting that many of them had sought a mother substitute rather than a partner. It is unnecessary to enlarge upon the suggestibility of miners to anyone conversant with the history of the industry.

This survey is incomplete without consideration of the deep psychological mechanisms involved, though in the absence of full analysis of individual patients, conclusions must be tentative.

Miners' nystagmus mainly involves the eyes, which play such an important part for the miner, both consciously and symbolically in his unconscious mind. So it may be suspected that the miners' potency phantasies are concerned. Such phantasies are built up in the infant during habit-training (Freud, 1936), for he finds that he can win approval or disapproval by evacuating or withholding his faeces at the proper time, and can thus control the attitude of the mother or nurse.

In keeping with the idea that miners' nystagmus involves potency phantasies, we see that half of the cases above have finally broken down when they felt that the work was such a strain that they could no longer cope with it. We find too that the miner can win approval or disapproval from the community as a whole—which occupies a similar position to that of the parent or nurse during infancy—by delivering or withholding coal from the bowels of the earth. A journey in a mine in the long subterranean, intestine-like galleries, makes this latter analogy particularly appropriate. It is significant too that most mining disputes arise over the question of production or wages; money being a well-known faecal symbol, familiarly expressed as " filthy lucre ", or even " dirty money ".

Putting all these observations together it is concluded that the collier is unconsciously preoccupied with power phantasies; and

breakdown is to be expected when these show signs of failing to be met, so that he feels impotent at his work. This postulate also explains the miner's sense of hostility to the community and the nature and frequency of colliery disputes. Thus a study of miners' nystagmus, a disease of darkness, has paradoxically, shed light on the very nature of the miner and his industrial relations.

Conclusions

(1) The precipitating cause of breakdown in miners' nystagmus is most often a feeling of inability to cope with the work, the deep psychological meaning of which is discussed, and next most often anxiety connected with the danger of the occupation.

(2) The conclusions of the previous paper are confirmed, as are its recommendations, and in particular, for the prevention of further cases of this intractable disorder, recommendation No. 8, that optimum hours of work in the mines should be worked out scientifically, and that this matter should be removed from the sphere of politics.

It is again a pleasure to thank Dr. Campbell for giving me facilities for this investigation. The expenses were defrayed by a grant from the British-Colliery Owners' Research Association, now merged in the National Coal Board.

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APPLIANCES

A NEW MODEL OF STREAK RETINOSCOPE*

BY

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THE first streak retinoscope, introduced by Wolff as early as 1896, was already a workable instrument. Subsequent models have, however, brought considerable technical improvements.

In that presented here, the manipulation can be effected with the hand holding the instrument. The diagram shows that the switch, the focussing of the beam, and the disk for rotating the streak are close to each other and within the reach of the same finger. Rotation of the cuff moves the projector lens up and down so that the beam can be adjusted to a plano or concave mirror-effect. The milled disk which serves for turning the filament, the image of which gives the streak, can be rotated clock-wise or anti-clock-wise without a stop. The movement is fast and the rotation of the streak from one principal meridian to the other is very easily carried out. There are two new features: an anti-glare hood to permit retinoscopy in daylight, and a scale indicating the position of the streak. If the instrument is held in a vertical position, and one principal meridian has already been corrected with spheres, the position of the streak indicates the axis of the cylinder, and can be read off the scale.

a, hood; *b*, cuff; *c*, milled disk.

The instrument is used in the same way as other streak retinoscopes. Two points, not widely known, are worth emphasizing:

(1) If in hypermetropia the less hypermetropic, and in myopia the more myopic, meridian is corrected and the plano mirror-effect is used, the streak indicating the axis is more sharply defined.

(2) In difficult cases of myopia the concave mirror-effect gives the clearer shadow movement.

The instrument is made by Messrs. C. W. Dixey, 9, Cavendish Square, London, W.1.

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FELLOWSHIPS

Travelling Awards in Ophthalmology and Otology, 1950-51

THE Medical Research Council invite applications for travelling awards for the academic year 1950-51 to be provided from the Alexander Pigott Wernher Memorial Trust, in accordance with a scheme approved by the trustees. Under the terms of the bequest, the funds are to be applied "towards the prevention and cure of blindness and deafness in the United Kingdom and British Empire, and in particular research in connection therewith by financing medical men and students within the Empire to study methods and practices in all countries of the world."

These awards are intended for suitably qualified medical graduates who have had some training in research work in ophthalmology or otology; in general, fellowships will be made for periods of up to a year for specific research purposes, but grants may also be given for short-term visits abroad to study particular methods of investigation and treatment in these fields. Fellowships will as a rule provide for appropriate subsistence allowance and travelling expenses, whereas grants for short-term visits (up to 3 months) will ordinarily cover travelling expenses only.

Forms of application for these awards may be obtained from the Secretary, Medical Research Council, 38 Old Queen Street, London, S.W.1, with whom applications should be lodged by June 1, 1950.